08/06/2006

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NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 4	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 5	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 6	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 7	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 8	JAN 30	Saved answer limit increased
NEWS 9	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 10	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 11	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 12	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 13	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 14	FEB 28	TOXCENTER reloaded with enhancements
NEWS 15	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 16	MAR 01	INSPEC reloaded and enhanced
NEWS 17	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 18	MAR 08	X.25 communication option no longer available after June 2006
NEWS 19	MAR 22	EMBASE is now updated on a daily basis
NEWS 20	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 21	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS 22	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS 23	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS 24	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS 25	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
http://download.cas.org/express/v8.0-Discover/

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that

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specific topic.

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* *

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In an effort to enhance your experience with STN, we would like to better understand what you find useful. Please take approximately 5 minutes to complete a web survey.

If you provide us with your name, login ID, and e-mail address, you will be entered in a drawing to win a free iPod(R). Your responses will be kept confidential and will help us make future improvements to STN.

Take survey: http://www.zoomerang.com/survey.zgi?p=WEB2259HNKWTUW

Thank you in advance for your participation.

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 09:21:32 ON 02 MAY 2006

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 09:21:37 ON 02 MAY 2006
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 1 MAY 2006 HIGHEST RN 882489-85-2
DICTIONARY FILE UPDATES: 1 MAY 2006 HIGHEST RN 882489-85-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *

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*   *
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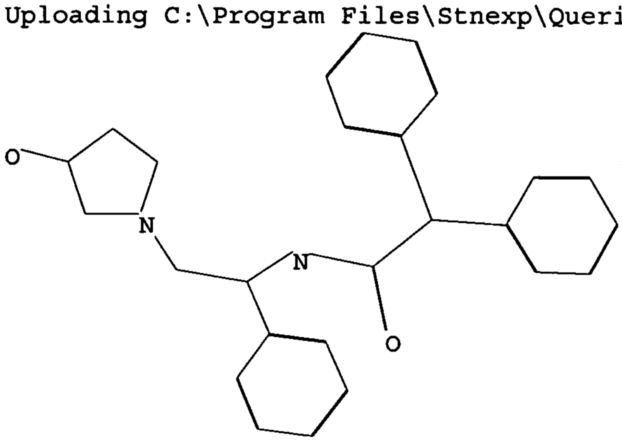
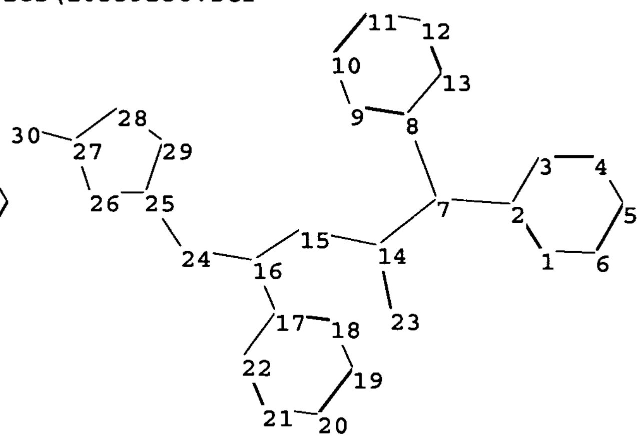
Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10539256.str





chain nodes :
7 14 15 16 23 24 30
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13 17 18 19 20 21 22 25 26 27 28 29
chain bonds :
2-7 7-8 7-14 14-15 14-23 15-16 16-17 16-24 24-25 27-30
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 17-18 17-22
18-19 19-20 20-21 21-22 25-26 25-29 26-27 27-28 28-29
exact/norm bonds :
14-15 14-23 15-16 24-25 25-26 25-29 26-27 27-28 27-30 28-29
exact bonds :
2-7 7-8 7-14 16-17 16-24
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13 17-18 17-22
18-19 19-20 20-21 21-22

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:CLASS 17:Atom 18:Atom 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:Atom 26:Atom 27:Atom 28:Atom
29:Atom 30:CLASS

L1   STRUCTURE UPLOADED

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=> d l1
L1 HAS NO ANSWERS
L1                STR
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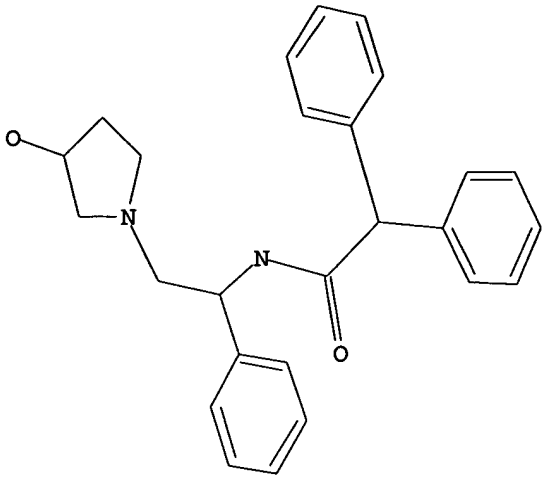


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Structure attributes must be viewed using STN Express query preparation.


=> s l1
SAMPLE SEARCH INITIATED 09:21:58 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -        7 TO ITERATE

100.0% PROCESSED         7 ITERATIONS                                 2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            7 TO      298
PROJECTED ANSWERS:               2 TO      124

L2             2 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 09:22:04 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      145 TO ITERATE

100.0% PROCESSED       145 ITERATIONS                               37 ANSWERS
SEARCH TIME: 00.00.01

L3            37 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   166.94     167.15

FILE 'HCAPLUS' ENTERED AT 09:22:12 ON 02 MAY 2006
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FILE COVERS 1907 - 2 May 2006 VOL 144 ISS 19
FILE LAST UPDATED: 1 May 2006 (20060501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l3
L4 58 L3

=> d ed abs ibib hitstr 1-58

L4 ANSWER 1 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 31 Mar 2006
AB The present invention relates to methods for regulating neurotransmitter systems by inducing a counteradaptation response. According to one embodiment of the invention, a method for regulating a neurotransmitter includes the step of repeatedly administering a ligand for a receptor in the neurotransmitter system, with a ratio of administration half-life to period between administrations of no greater than 1/2. The methods of the present invention may be used to address a whole host of undesirable mental and neurol. conditions.

ACCESSION NUMBER: 2006:301807 HCAPLUS
DOCUMENT NUMBER: 144:343618
TITLE: Methods for regulating neurotransmitter systems by inducing counteradaptations
INVENTOR(S): Michalow, Alexander
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006034343	A2	20060330	WO 2005-US33826	20050923

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH,

GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 2006069086 A1 20060330 US 2005-234850 20050923

PRIORITY APPLN. INFO.: US 2004-612155P P 20040923

IT **153205-46-0**, Asimadoline

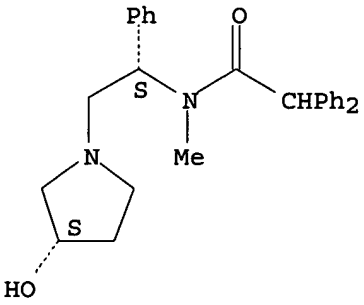
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(regulating neurotransmitter systems by inducing counteradaptations by repeatedly administering neurotransmitter receptor ligands to treat mental and neurol. disorders and combination with other agents)

RN 153205-46-0 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ED Entered STN: 19 Feb 2006

AB The use of classification trees for modeling and predicting the passage of mols. through the blood-brain barrier was evaluated. The models were built and evaluated using a data set of 147 mols. extracted from the literature. In the first step, single classification trees were built and evaluated for their predictive abilities. In the second step, attempts were made to improve the predictive abilities using a set of 150 classification trees in a boosting approach. Two boosting algorithms, discrete and real adaptive boosting, were used and compared. High-predictive classification trees were obtained for the data set used, and the models could be improved with boosting. In the context of this research, discrete adaptive boosting gives slightly better results than real adaptive boosting.

ACCESSION NUMBER: 2006:152812 HCAPLUS

TITLE: Classification Tree Models for the Prediction of Blood-Brain Barrier Passage of Drugs

AUTHOR(S): Deconinck, Eric; Zhang, Menghui H.; Coomans, Danny; Vander Heyden, Yvan

CORPORATE SOURCE: Department of Analytical Chemistry and Pharmaceutical Technology Pharmaceutical Institute, Vrije Universiteit Brussel-VUB, Brussels, B-1090, Belg.

SOURCE: Journal of Chemical Information and Modeling ACS ASAP CODEN: JCISD8; ISSN: 1549-9596

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

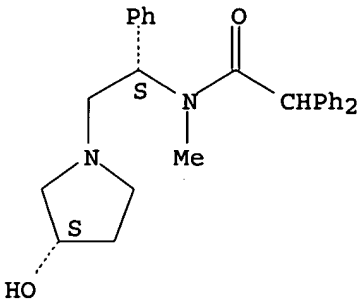
IT INDEXING IN PROGRESS

IT **153205-46-0**, Asimadoline

RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological

study); USES (Uses)
(classification tree models for prediction of blood-brain barrier passage of drugs)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 03 Feb 2006
AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.
ACCESSION NUMBER: 2006:100738 HCAPLUS
DOCUMENT NUMBER: 144:198849
TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients
INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar
PATENT ASSIGNEE(S): India
SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2006024365	A1	20060202	US 2005-134633		20050519
US 2004096499	A1	20040520	US 2003-630446		20030729
PRIORITY APPLN. INFO.:			IN 2002-MU697	A	20020805
			IN 2002-MU699	A	20020805
			IN 2003-MU80	A	20030122
			IN 2003-MU82	A	20030122
			US 2003-630446	A2	20030729

IT **153205-46-0**, Asimadoline

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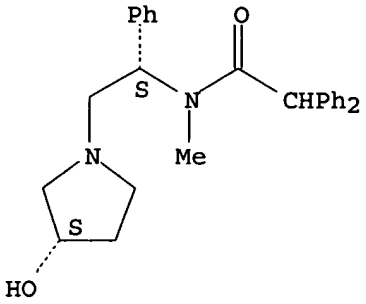
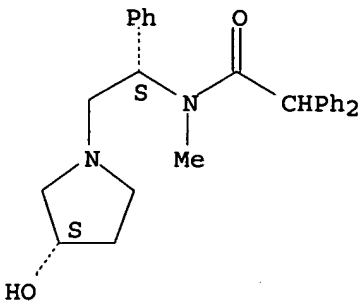
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel dosage form comprising modified-release and immediate-release active ingredients)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 4 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 26 Oct 2005
AB Unavailable
ACCESSION NUMBER: 2005:1144762 HCAPLUS
DOCUMENT NUMBER: 143:359960
TITLE: Clinical study for evaluation of the analgetic effect of the orally administered k-opioid agonist Asimadoline (EMD 61753) after post operative intervention to the lower extremities (phase IIa pilot study)
AUTHOR(S): Paprotny, Margarete
CORPORATE SOURCE: Germany
SOURCE: (2003) No pp., given, http://www.meind.de/search.py?18586 Avail.: Metadata on Internet Documents, Order No. 18586
From: Metadata Internet Doc. [Ger. Diss.] 2003, (D1021-1), No pp. given
DOCUMENT TYPE: Dissertation
LANGUAGE: German
IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Clin. study for evaluation of the analgetic effect of the orally administered k-opioid agonist Asimadoline (EMD 61753) after post operative intervention to the lower extremities (phase IIa pilot study))
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 5 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 19 Aug 2005
AB The invention relates to the combination of (S)-pantoprazole and/or its salts and compds., which modify gastrointestinal motility. The invention relates to the combination of (1) a first ingredient (S)-pantoprazole and/or its salts and (2) a second active ingredient, which modifies gastrointestinal motility, selected from a group consisting of 5-HT agonists/antagonists, muscarinic antagonists, κ-opioid receptor agonists, δ-opioid receptor agonists, opioid receptor agonists, dopamine receptor antagonists, cholecystokinin A antagonists, α2 adrenoceptor agonists, N-methyl-D-aspartate receptor antagonists, non-N-methyl-D-aspartate glutamate receptor antagonists, nitric oxide synthase inhibitors, motilin agonists, somatostatin agonists/antagonists, neurotensin agonists/antagonists, vasoactive intestinal peptide antagonists, substance P antagonists, neurokinin antagonists, calcium channel blockers, potassium channel openers, selective serotonin reuptake inhibitors, corticotropin releasing factor antagonists, GABA-A receptor agonists, GABA-B receptor agonists, gastroprokinetics, antiemetics and antispasmodics.

ACCESSION NUMBER: 2005:823572 HCAPLUS
DOCUMENT NUMBER: 143:199942
TITLE: Pharmaceutical combinations comprising (S)-pantoprazole
INVENTOR(S): Huber, Reinhard; Kohl, Bernhard; Kromer, Wolfgang; Simon, Wolfgang-Alexander
PATENT ASSIGNEE(S): Altana Pharma A.-G., Germany
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005074931	A1	20050818	WO 2005-EP50336	20050127

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,

RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

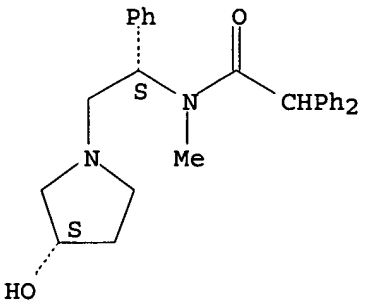
PRIORITY APPLN. INFO.: EP 2004-1757 A 20040128

IT **153205-46-0**, ASIMADOLINE
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical combinations comprising pantoprazole and gastrointestinal motility modifiers)

RN 153205-46-0 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ED Entered STN: 27 May 2005

AB The invention discloses the use of compds. that are effective as selective opiate receptor modulators for the manufacture of a pharmaceutical for the diagnosis, prophylaxis and/or the treatment of neuropathy, the clin. pictures and symptoms associated therewith, and related disorders. Also disclosed are pharmaceutical compns. comprising one or more of the modulator compds.

ACCESSION NUMBER: 2005:451198 HCAPLUS

DOCUMENT NUMBER: 142:457128

TITLE: Use of selective opiate receptor modulators in the treatment of neuropathy

INVENTOR(S): Bartoszyk, Gerd

PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany

SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005046687	A1	20050526	WO 2004-EP11548	20041014

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

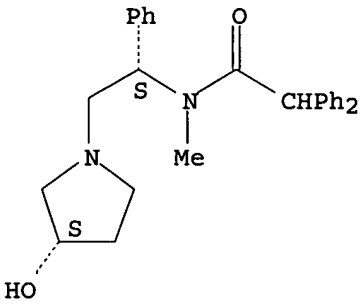
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2003-24781 A 20031030

IT **153205-46-0 153205-46-0D**, derivs. **185951-07-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opiate receptor modulators for neuropathy treatment)

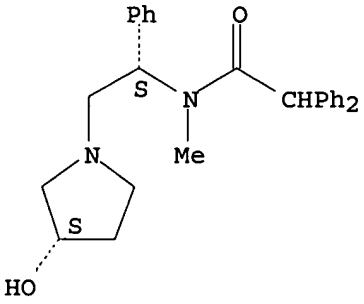
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



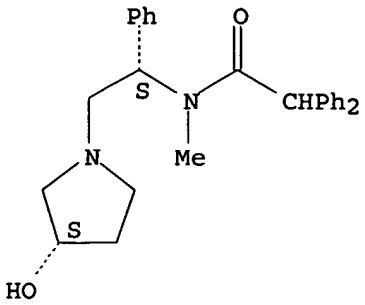
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 185951-07-9 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



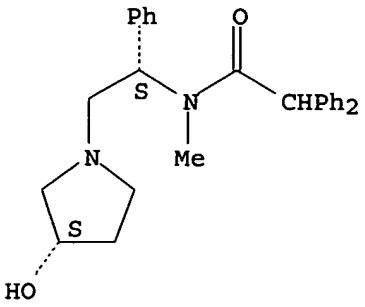
● HCl

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 17 May 2005
AB As well as previous two reports, opioid analgesics are analyzed by the method of computer chemical Except for fentanyl and methadone, opioid analgesics have rigid or non-transformed mol. structures. Opioid receptor models were put forward by Beckette and others. A plane composed of an isoquinoline ring and benzene C ring was perpendicular to the mol. axis in the models. Neg. charge localized at hydroxyl group of the benzene A ring in the models. On the other hand, our calcn. showed that the neg. charge delocalized to π orbital of the benzene A ring. μ Agonist had protrusion on the same side of oxygen bridge in the mol. The protrusion of μ antagonist localized on the reverse side. Each characteristics of δ and κ agonists and antagonists is detailed in this text.
The multiple regression anal. showed that the multiple correlation coefficient was a little low value, taking the physico-chemical-structural indexes as independent variables.
ACCESSION NUMBER: 2005:417198 HCAPLUS
DOCUMENT NUMBER: 143:70977
TITLE: Characteristics of drugs evaluated by computational chemistry (3) Opioids
AUTHOR(S): Hayano, Taizo; Kishioka, Shiroh; Yamamoto, Hiroyuki; Ikoma, Yoshihisa
CORPORATE SOURCE: Div. Psychiatry, Asahikai Wakaura Hosp., Japan
SOURCE: Wakayama Igaku (2005), 56(1), 5-9
CODEN: WKMIAO; ISSN: 0043-0013
PUBLISHER: Wakayama Igakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
IT **153205-46-0**, EMD-61753
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characteristics and mol. structure of opioids and their antagonits evaluated by computational chemical)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Young, Shawquia



L4 ANSWER 8 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 13 Jan 2005
AB A medical drug capable of inhibiting the fall of pain threshold. In particular, a κ-opioid receptor agonist is capable of effectively inhibiting the fall of pain threshold, so that it is useful as a pain threshold fall inhibitor.

ACCESSION NUMBER: 2005:29228 HCAPLUS
DOCUMENT NUMBER: 142:107431
TITLE: Pain threshold fall inhibitor
INVENTOR(S): Shimomura, Kyoichi; Aono, Hiroyuki; Tsukahara, Yaeko; Hata, Taeko
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005002622	A1	20050113	WO 2004-JP9766	20040702
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2005041866	A2	20050217	JP 2004-196146	20040702
EP 1642590	A1	20060405	EP 2004-747234	20040702
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.: JP 2003-270967 A 20030704
WO 2004-JP9766 W 20040702

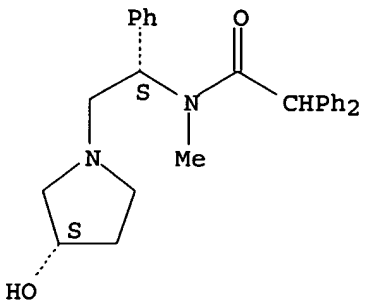
OTHER SOURCE(S): MARPAT 142:107431

IT **185951-07-9**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(κ-opioid receptor agonists as pain threshold fall inhibitors)

RN 185951-07-9 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-

N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 10 Dec 2004
AB The invention relates to the combination of certain active compds. from the acid pump antagonist class and compds. which modify gastrointestinal motility. The acid pump antagonist class is selected from a tricyclic imidazopyridine and the gastrointestinal motility modifier is selected from a 5-HT-(partial)-agonist/antagonist.
ACCESSION NUMBER: 2004:1059201 HCAPLUS
DOCUMENT NUMBER: 142:32977
TITLE: Pharmaceutical combinations of a proton pump inhibitor and a compound which modifies gastrointestinal motility
INVENTOR(S): Zimmermann, Peter Jan; Chiesa, M. Vittoria; Palmer, Andreas; Brehm, Christof; Klein, Thomas; Senn-Bilfinger, Joerg; Simon, Wolfgang-Alexander; Kromer, Wolfgang; Grundler, Gerhard; Hanauer, Guido; Buhr, Wilm; Postius, Stefan
PATENT ASSIGNEE(S): Altana Pharma A.-G., Germany
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004105795	A1	20041209	WO 2004-EP50936	20040526

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

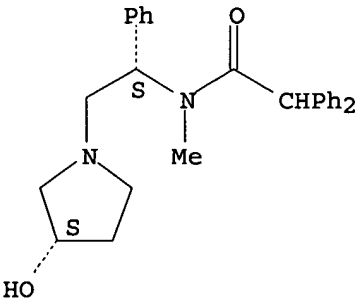
AU 2004243444	A1	20041209	AU 2004-243444	20040526
CA 2526566	AA	20041209	CA 2004-2526566	20040526
EP 1644043	A1	20060412	EP 2004-741658	20040526

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

PRIORITY APPLN. INFO.:
EP 2003-11875 A 20030527
EP 2004-102304 A 20040525
WO 2004-EP50936 W 20040526

IT **153205-46-0**, Asimadoline
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical combinations of proton pump inhibitor and modifier of gastrointestinal motility)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 28 Oct 2004
AB Stable pharmaceutical compns. useful for administering methylnaltrexone are described. Kits, including these pharmaceutical compns., also are provided. Thus, a formulation for s.c. administration contained methynaltrexone 30, NaCl 4, citric acid 0.0875, trisodium citrate 0.0496, and disodium edetate 0.75 mg and water for injection qs to 1 g.

ACCESSION NUMBER: 2004:902190 HCAPLUS
DOCUMENT NUMBER: 141:370575
TITLE: Pharmaceutical formulations containing methylnaltrexone
INVENTOR(S): Sanghvi, Suketu P.; Boyd, Thomas A.
PATENT ASSIGNEE(S): Progenics Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004091623	A1	20041028	WO 2004-US10997	20040408

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

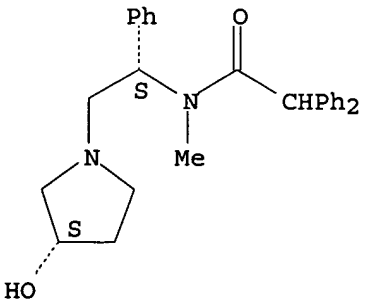
AU 2004229463	A1	20041028	AU 2004-229463		20040408
CA 2521379	AA	20041028	CA 2004-2521379		20040408
US 2004266806	A1	20041230	US 2004-821811		20040408
EP 1615646	A1	20060118	EP 2004-759349		20040408

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR

PRIORITY APPLN. INFO.:	US 2003-461611P	P	20030408
	WO 2004-US10997	W	20040408

IT **153205-46-0**, Asimadoline
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulations containing methylnaltrexone)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



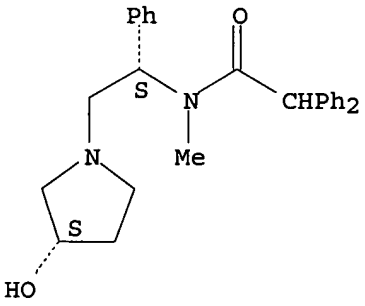
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 27 Oct 2004
AB The potent κ-opioid receptor agonist n-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)-ethyl]-2,2-diphenyl-acetamide hydrochloride (asimadoline, EMD 61753) was initially developed for the treatment of chronic pain. Because opioids are well known to reduce secretion and to cause constipation, we investigated the effects on epithelial transport in murine trachea and colon. In Ussing chamber expts., asimadoline (100 μM) decreased short-circuit currents in airways and colon epithelium. The inhibition of ISC was not blocked by naloxone (10 μM) or nor-binaltorphimine (10 μM), suggesting that the response was not mediated by κ-opioid receptors. The effect of asimadoline on ISC was concentration-dependent with half-maximal inhibition of ISC at 23.7 (9.5 - 49.3) μM and was sensitive to the K+ channel blocker charybdotoxin (10 nM). The amiloride-sensitive Na+ current was reduced by asimadoline, but not in cAMP stimulated tissues. Asimadoline strongly

inhibited transient Ca2+-dependent Cl- secretion, activated by the muscarinic receptor agonist carbachol (100 μM) or the purinergic agonist ATP (100 μM). Thus, asimadoline inhibits epithelial transport independent of κ-opioid receptors, by inhibition of basolateral Ca2+-activated and charybdotoxin-sensitive K+ channels.

ACCESSION NUMBER: 2004:892405 HCAPLUS
DOCUMENT NUMBER: 141:388440
TITLE: The κ-opioid receptor agonist asimadoline inhibits epithelial transport in mouse trachea and colon
AUTHOR(S): Schreiber, Rainer; Bartoszyk, Gerd D.; Kunzelmann, Karl
CORPORATE SOURCE: Institut fuer Physiologie, Universitaet Regensburg, Regensburg, D-93053, Germany
SOURCE: European Journal of Pharmacology (2004), 503(1-3), 185-190
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(κ-opioid receptor agonist asimadoline inhibits epithelial transport in mouse trachea and colon)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 26 Aug 2004
AB A review. The therapeutic management of functional dyspepsia remains a major challenge for the gastroenterologist. Current therapies available are based on putative underlying pathophysiol. mechanisms, including gastric acid sensitivity, slow gastric emptying and Helicobacter pylori infection, but only a small proportion of patients achieve symptomatic benefit from these therapeutic approaches. Relatively novel mechanistic concepts under testing include impaired gastric accommodation, visceral hypersensitivity, and central nervous system dysfunction. Serotonergic modulators (e.g. the 5-HT4 agonist tegaserod, the 5-HT3 antagonist alosetron and the 5-HT1P agonist sumatriptan), CCK-1 antagonists (e.g. dexloxiglumide), opioid agonists (e.g. asimadoline), N-methyl-D-aspartate

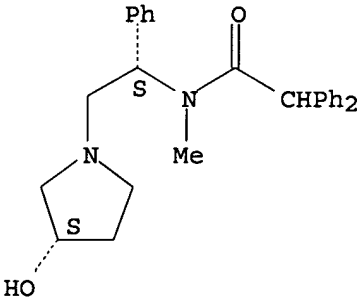
(NMDA) receptor antagonists (e.g dextromethorphan), neurokinin antagonists (e.g. talnetant), capsaicin-like agents and antidepressants are among the agents currently under investigation. It seems unlikely, however, that targeting a single mechanism with an individual drug will result in complete symptom remission in most cases.

ACCESSION NUMBER: 2004:694639 HCAPLUS
DOCUMENT NUMBER: 142:106268
TITLE: Functional dyspepsia: drugs for new (and old) therapeutic targets
AUTHOR(S): Cremonini, Filippo; Delgado-Aros, Silvia; Talley, Nicholas J.
CORPORATE SOURCE: Clinical Enteric Neuroscience Translational and Epidemiological Research Program, Mayo Clinic College of Medicine, Rochester, MN, 55905, USA
SOURCE: Best Practice & Research, Clinical Gastroenterology (2004), 18(4), 717-733
CODEN: BPRCB6
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(opioid agonist asimadoline can be used as therapeutic agent for treatment of functional dyspepsia in human)

RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



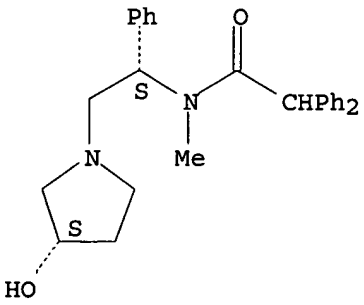
REFERENCE COUNT: 116 THERE ARE 116 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 25 Aug 2004
AB Visceral hypersensitivity plays a major role in irritable bowel syndrome pathophysiol. Opioid κ receptors on afferent nerves may modulate it and be the target for new irritable bowel syndrome treatments. This study evaluated the effect of the κ opioid agonist asimadoline on perception of colonic distension and colonic compliance in irritable bowel syndrome patients. Twenty irritable bowel syndrome female patients (Rome II criteria; 40±13 yr) and hypersensitivity to colonic distension (Pain threshold ≤ 32 mmHg) were included in a randomized double-blind cross-over trial comparing the effect of a single oral dose of asimadoline 0.5 mg or placebo on sensory thresholds (defined as a constant and sustained

sensation) elicited by left colon phasic distension (5 mmHg steps, 5 min) up to a sensation of abdominal pain. Colonic compliance was compared by the slope of the pressure-volume curves. On asimadoline, pain threshold (mean ± s.d.) (29.8±7.2 mmHg) was higher than on placebo (26.3±7.8 mmHg), difference not statistically significant (P = 0.1756, ANOVA). Area under curve of pain intensity rated at each distension step was significantly lower on asimadoline (89.3±33.9, ANOVA) than on placebo (108.1±29.7) (P = 0.0411). Thresholds of perception of nonpainful distensions were not altered on asimadoline, as compared with placebo. Colonic compliance was not different on placebo and asimadoline. Asimadoline decreases overall perception of pain over a wide range of pressure distension of the colon in irritable bowel syndrome patients, without altering its compliance. These data suggest that further studies should explore the potential benefit of asimadoline in treatment of pain in irritable bowel syndrome patients.

ACCESSION NUMBER: 2004:690976 HCAPLUS
DOCUMENT NUMBER: 141:254206
TITLE: Effect of asimadoline, a κ opioid agonist, on pain induced by colonic distension in patients with irritable bowel syndrome
AUTHOR(S): Delvaux, M.; Beck, A.; Jacob, J.; Bouzamondo, H.; Weber, F. T.; Frexinos, J.
CORPORATE SOURCE: Gastroenterology Department, CHU Rangueil, Toulouse, Fr.
SOURCE: Alimentary Pharmacology and Therapeutics (2004), 20(2), 237-246
CODEN: APTHEN; ISSN: 0269-2813
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of asimadoline on pain induced by colonic distension in patients with irritable bowel syndrome)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 01 Jul 2004
AB N-methyl-N-[(1S)-1-phenyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]ethyl]-2,2-di-

phenylacetamide with ≥1 covalently bound acids and the salts, solvates, and prodrugs thereof, were prepared for treatment of pain, inflammation, obesity, anorexia, dysorexia, gastroparesis, dysponderosis, etc. (no data). Thus, N-methyl-N-[(1S)-1-phenyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]ethyl]-2,2-diphenylacetamide hydrochloride was warmed with Ac2O and Et3N for 2 h on a steam bath to give N-[2-[(3S)-3-acetoxy-2-pyrrolidinyl]-(1S)-1-phenylethyl]-2,2-diphenyl-N-methylacetamide.

ACCESSION NUMBER: 2004:525892 HCAPLUS
DOCUMENT NUMBER: 141:89002
TITLE: Preparation of asimadoline derivatives with covalently bound acids as opiate receptor agonists
INVENTOR(S): Seyfried, Christoph; Wiesner, Matthias
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: Ger. Offen., 20 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10259245	A1	20040701	DE 2002-10259245	20021217
CA 2510167	AA	20040701	CA 2003-2510167	20031125
WO 2004054970	A1	20040701	WO 2003-EP13206	20031125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003288159	A1	20040709	AU 2003-288159	20031125
EP 1572640	A1	20050914	EP 2003-780043	20031125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006511521	T2	20060406	JP 2004-559717	20031125

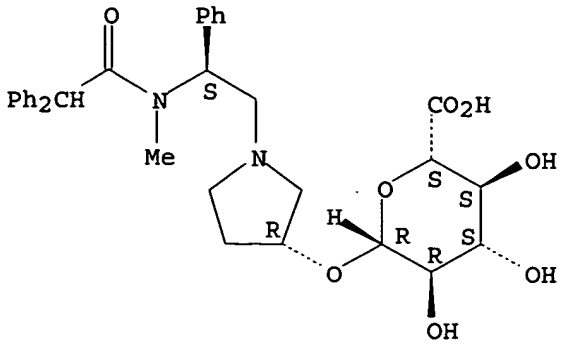
PRIORITY APPLN. INFO.: DE 2002-10259245 A 20021217
WO 2003-EP13206 W 20031125

OTHER SOURCE(S): MARPAT 141:89002

IT **714237-71-5P 714237-72-6P 714237-73-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(claimed compound; preparation of asimadoline derivs. with covalently bound acids as opiate receptor agonists)

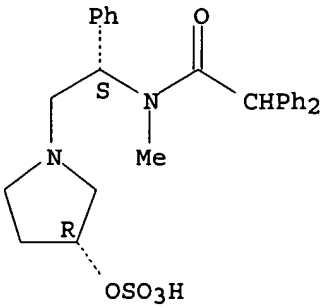
RN 714237-71-5 HCAPLUS
CN β-D-Glucopyranosiduronic acid, (3R)-1-[(2S)-2-[(diphenylacetyl)methylamino]-2-phenylethyl]-3-pyrrolidinyl (9CI) (CA INDEX NAME)

Absolute stereochemistry.



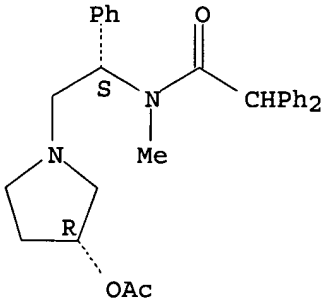
RN 714237-72-6 HCAPLUS
CN Benzeneacetamide, N-methyl-α-phenyl-N-[(1S)-1-phenyl-2-[(3R)-3-(sulfooxy)-1-pyrrolidinyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 714237-73-7 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3R)-3-(acetyloxy)-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

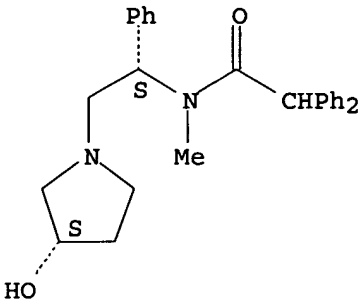
Absolute stereochemistry.



IT **153205-46-0DP**, Asimadoline, covalently bound acid derivs.
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of asimadoline derivs. with covalently bound acids as opiate receptor agonists)
RN 153205-46-0 HCAPLUS

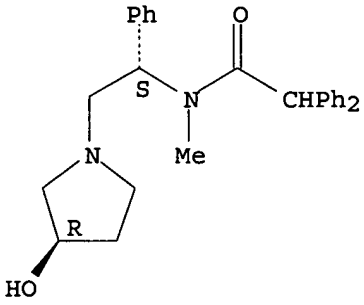
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **714237-75-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of asimadoline derivs. with covalently bound acids as opiate receptor agonists)
RN 714237-75-9 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3R)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

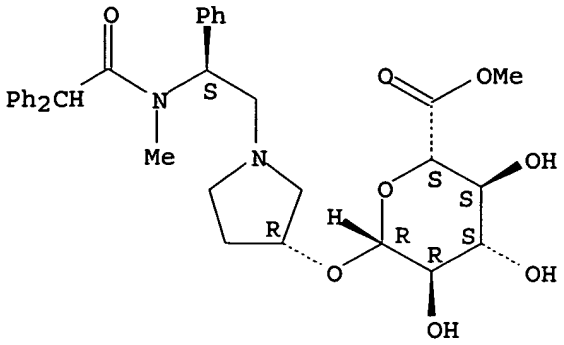
Absolute stereochemistry.



● HCl

IT **714237-74-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of asimadoline derivs. with covalently bound acids as opiate receptor agonists)
RN 714237-74-8 HCAPLUS
CN β-D-Glucopyranosiduronic acid, (3R)-1-[(2S)-2-[(diphenylacetyl)methylamino]-2-phenylethyl]-3-pyrrolidinyl, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 15 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 28 Nov 2003
AB The instant invention relates to the use of compds. that are effective as selective opiate receptor modulators for the manufacture of pharmaceuticals for the diagnosis and/or the treatment of disorders, said disorders being selected from eating disorders and digestive disorders, especially psychogenic eating disorders, for the manufacture of a pharmaceutical effective for modulating the gastrointestinal tonus, and to pharmaceutical composition, comprising one or more of said modulator compds. and one or more compds. that are effective as appetite depressant.

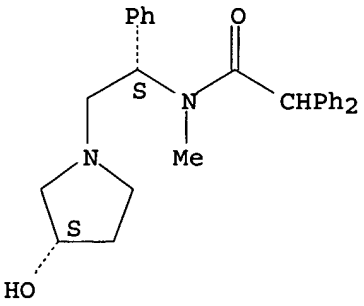
ACCESSION NUMBER: 2003:931175 HCAPLUS
DOCUMENT NUMBER: 139:391378
TITLE: Use of compounds that are effective as selective opiate receptor modulators
INVENTOR(S): Weber, Frank; Jacob, Jutta; Barber, Andrew; Gottschlich, Rudolf
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003097051	A2	20031127	WO 2003-EP4428	20030428
WO 2003097051	A3	20041209		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2486000	AA	20031127	CA 2003-2486000	20030428
AU 2003242527	A1	20031202	AU 2003-242527	20030428
EP 1505974	A2	20050216	EP 2003-752716	20030428
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003009969	A	20050426	BR 2003-9969	20030428

US 2005176746	A1	20050811	US 2003-514887		20030428
CN 1655784	A	20050817	CN 2003-811137		20030428
JP 2005531557	T2	20051020	JP 2004-505050		20030428
ZA 2004010160	A	20051020	ZA 2004-10160		20041215
PRIORITY APPLN. INFO.:			EP 2002-11047	A	20020517
			WO 2003-EP4428	W	20030428

IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(selective opiate receptor modulators for treatment of eating and digestive disorders)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

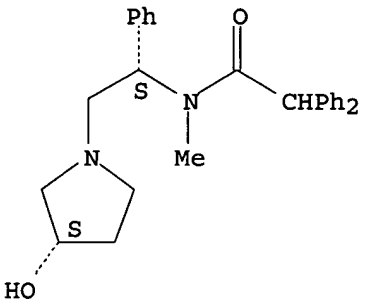


L4 ANSWER 16 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 22 Oct 2003
AB Aim: To evaluate the effect of single administrations of asimadoline, a κ-opioid agonist, on satiation volume, postprandial symptoms and gastric vols. Methods: Healthy subjects received oral placebo, or 0.5 or 1.5 mg asimadoline in a randomized, double-blind fashion 1 h prior to testing. We assessed effects on the volume of Ensure to achieve full satiation and postprandial symptoms 30 min after meal, and on gastric volume (fasting and postprandial) measured by 99mTc-single photon emission tomog. (SPECT) imaging. Results: Thirteen healthy subjects were studied in each treatment arm. Compared to placebo, asimadoline 0.5 mg decreased postprandial fullness without affecting the volume ingested at full satiation. Asimadoline 1.5 mg decreased satiation during meal, allowing increased satiation vols. and tended to decrease postprandial fullness, despite higher vols. ingested. There was a significant treatment-gender interaction in the effect of asimadoline on gastric vols. Asimadoline 0.5 mg (not 1.5 mg) increased fasting and postprandial gastric vols. in females but decreased fasting vols. in males. The effect of asimadoline on gastric volume did not explain the effect observed on satiation volume or postprandial fullness. Conclusion: A single oral administration of asimadoline decreases satiation and postprandial fullness in humans independently of its effects on gastric volume
ACCESSION NUMBER: 2003:827955 HCAPLUS
DOCUMENT NUMBER: 140:192846
TITLE: Effects of asimadoline, a κ-opioid agonist, on satiation and postprandial symptoms in health
AUTHOR(S): Delgado-Aros, S.; Chial, H. J.; Cremonini, F.; Ferber, I.; McKinzie, S.; Burton, D. D.; Camilleri, M.
CORPORATE SOURCE: Clinical Enteric Neuroscience Translational and

Epidemiological Research Program, Rochester, MN, USA
SOURCE: Alimentary Pharmacology and Therapeutics (2003), 18(5), 507-514
CODEN: APTHEN; ISSN: 0269-2813
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); BIOL (Biological study)
(asimadoline effect on satiation and postprandial fullness in humans independent of effects on gastric volume)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



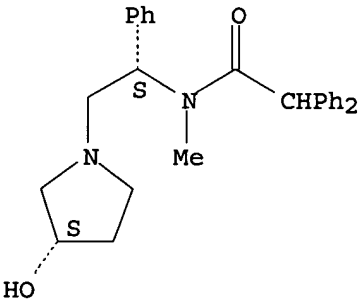
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 03 Oct 2003
AB We have previously reported that U50,488 [(trans-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]benzeneacetamide] enantiomers contribute to visceral antinociception by a nonopioid receptor-mediated blockade of sodium currents in colon sensory neurons. The present expts. were undertaken to examine the effect of arylacetamide κ-opioid receptor agonists (κ-ORAs) U50,488 and EMD 61,753 [(N-methyl-N-[1S)-1-phenyl)-2-(13S))-3-hydroxypyrrolidine-1-yl)-ethyl]-2,2-diphenylacetamide HCl] on tetrodotoxin-sensitive (TTX-S) and -resistant (TTX-R) sodium currents, and the mechanism of their sodium channel-blocking actions. Whole cell patch-clamp expts. were performed on colon sensory neurons from the S1 dorsal root ganglion identified by content of retrograde tracer 1.1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine metanesulfonate. The concentration-response curves of U50,488 and EMD 61,753, for tonic inhibition of total, TTX-S, and TTX-R sodium currents were similar (EC50 values for U50,488 and EMD 61,753 were 8.4±1.69 and 1.2±1.78 μM, resp.). In contrast, the peptide κ-ORA dynorphin was without effect in these expts. U50,488 (10 μM) shifted the voltage dependence of steady-state inactivation curves for total, TTX-S, and TTX-R currents to more neg. potentials. Inhibition was present at holding potentials of -100 to -20 mV. After the tonic block elicited by 10 μM U50,488, repetitive stimulation with 5-ms depolarizing pulses at a frequency of 3 Hz further enhanced the inhibition of total, TTX-R, and TTX-S currents by 43.8±4.9, 46.2±4.9, and 40±3.2%, resp. These results demonstrate that arylacetamide κ-ORAs nonselectively inhibit voltage-evoked

sodium currents in a manner similar to local anesthetics, by enhancing closed-state inactivation and induction of use-dependent block.

ACCESSION NUMBER: 2003:775803 HCAPLUS
DOCUMENT NUMBER: 140:87591
TITLE: Arylacetamide κ-opioid receptor agonists produce a tonic-and use-dependent block of tetrodotoxin-sensitive and -resistant sodium currents in colon sensory neurons
AUTHOR(S): Joshi, S. K.; Lamb, Kenneth; Bielefeldt, K.; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, Roy J. and Lucille A. Carver College of Medicine, The University of Iowa, Iowa City, IA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 307(1), 367-372
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(arylacetamide κ-ORA blockade of tetrodotoxin-sensitive and -resistant sodium currents in colon sensory neurons)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



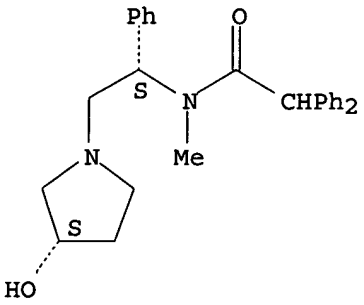
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 01 Oct 2003
AB A review examining the antiinflammatory effects of κ-opioids, both centrally active and peripherally selective κ-opioid agonists, with particular relevance to rheumatoid arthritis. Data on mechanisms responsible for the anti-arthritic effects of κ-opioids in adjuvant arthritis are presented.
ACCESSION NUMBER: 2003:765822 HCAPLUS
DOCUMENT NUMBER: 140:280486
TITLE: Anti-inflammatory effects of opioids
AUTHOR(S): Walker, Judith S.
CORPORATE SOURCE: School of Physiology and Pharmacology, University of New South Wales, Sydney, Australia

08/06/2006

SOURCE: Advances in Experimental Medicine and Biology (2003), 521(Immune Mechanisms of Pain and Analgesia), 148-160
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiinflammatory effects of κ-opioids in arthritis)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

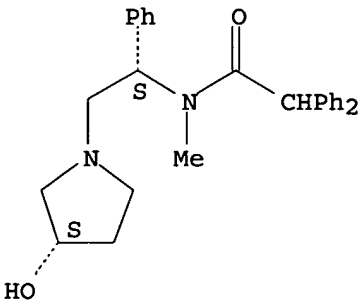
L4 ANSWER 19 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 04 Jul 2003
AB In order to develop potent and selective peripheral κ-agonists with long duration of action in vivo, the authors prepared a series of secondary and tertiary tetrapeptide amides based on H-D-Phe-D-Phe-D-Nle-D-Arg-NH2 (FE 200041) and tested them in vitro as well as for antinociceptive potency in the mouse acetic acid writhing test (mWT), and for sedation in the mouse rotarod test (mRT). The studies showed that two of the peptides, H-D-Phe-D-Phe-D-Nle-D-Arg-NH-4-Pic (FE 200665) and H-D-Phe-D-Phe-D-Leu-D-Orn-morpholine amide (FE 200666), appear to be promising drug candidates with high affinity and selectivity at KOR, high antinociceptive potency in vivo, and unprecedented peripheral selectivity. Structure activity relationship for the series of peptides tested is discussed.
ACCESSION NUMBER: 2003:509744 HCAPLUS
DOCUMENT NUMBER: 140:52749
TITLE: Long acting, selective, peripheral kappa agonists
AUTHOR(S): Wisniewski, Kazimierz; Sueiras-Diaz, Javier; Schteingart, Claudio; Galyean, Robert; Houghten, Richard; Vanderah, Todd; Porreca, Frank; Riviere, Pierre; Junien, Jean Louis; Trojnar, Jerzy
CORPORATE SOURCE: Ferring Research Institute Inc., San Diego, CA, 92121, USA
SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 775-776. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.

Young, Shawquia

CODEN: 69EDWK; ISBN: 2-84254-048-4
DOCUMENT TYPE: Conference
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison compound; long acting, selective, peripheral kappa agonists tetrapeptides as analgesics)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



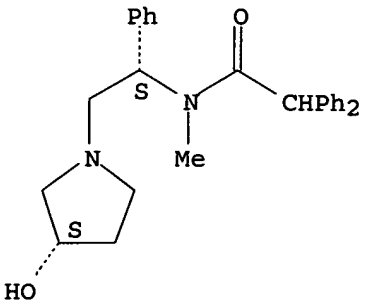
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 11 Jun 2003
AB The PharMingen KA8 antibody discussed in the 10th paragraph of Materials and Methods should have been listed as a PharMingen polyclonal antibody.

ACCESSION NUMBER: 2003:444402 HCAPLUS
DOCUMENT NUMBER: 139:79032
TITLE: κ-opioid receptor agonists modulate visceral nociception at a novel, peripheral site of action. [Erratum to document cited in CA133:217585]
AUTHOR(S): Joshi, S. K.; Su, Xin; Porreca, Frank; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Neuroscience (2002), 22(5), 2012
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **153205-46-0**, EMD 61753
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(κ-opioid receptor agonists modulate visceral nociception at novel, peripheral site of action (Erratum))
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

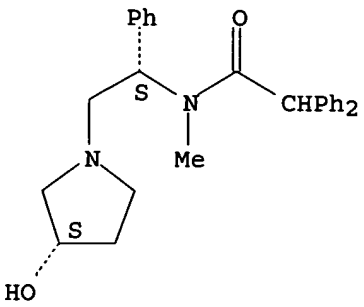


L4 ANSWER 21 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 05 May 2003
AB To compare the effects of the κ-opioid agonist asimadoline and placebo on visceral sensation and gastrointestinal (GI) motor functions in humans, 91 healthy participants were randomized in a double-blind fashion to 0.15, 0.5, or 1.5 mg of asimadoline or placebo orally twice a day for 9 days. We assessed satiation (nutrient drink test), colonic compliance, tone, perception of colonic distension (barostat), and whole gut transit (scintigraphy). Treatment effect was assessed by anal. of covariance. Asimadoline increased nutrient drink intake (P = 0.03). Asimadoline decreased colonic tone during fasting (P = 0.03) without affecting postprandial colonic contraction, compliance, or transit. Gas scores in response to colonic distension were decreased with 0.5 mg of asimadoline at low levels (8 mmHg above operating pressure) of distension (P = 0.04) but not at higher levels of distension. Asimadoline at 1.5 mg increased gas scores at 16 mmHg of distension (P = 0.03) and pain scores at distensions of 8 and 16 mmHg (P = 0.003 and 0.03, resp.) but not at higher levels of distension. Further studies of this compound in diseases with altered satiation or visceral sensation are warranted.

ACCESSION NUMBER: 2003:338799 HCAPLUS
DOCUMENT NUMBER: 139:173690
TITLE: Effects of a κ-opioid agonist, asimadoline, on satiation and GI motor and sensory functions in humans
AUTHOR(S): Delgado-Aros, Silvia; Chial, Heather J.; Camilleri, Michael; Szarka, Lawrence A.; Weber, Frank T.; Jacob, Jutta; Ferber, Irene; McKinzie, Sanna; Burton, Duane D.; Zinsmeister, Alan R.
CORPORATE SOURCE: Clinical Enteric Neuroscience Translational and Epidemiological Research Program, Mayo Clinic, Rochester, MN, 55905, USA
SOURCE: American Journal of Physiology (2003), 284(4, Pt. 1), G558-G566
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of a κ-opioid agonist, asimadoline, on satiation and GI motor and sensory functions in humans)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

08/06/2006

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 10 Oct 2002
AB The invention concerns the use of asimadoline or its pharmacol. acceptable salts for the production of drug formulations to treat bladder diseases, in particular the pain associated with irritated bladder syndrome.
ACCESSION NUMBER: 2002:772119 HCAPLUS
DOCUMENT NUMBER: 137:257701
TITLE: Kappa opiate agonist asimadoline for the treatment of bladder diseases especially irritable bladder syndrome
INVENTOR(S): Jacob, Jutta; Weber, Frank; Bartoszyk, Gerd; Seyfried, Christoph
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 4 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

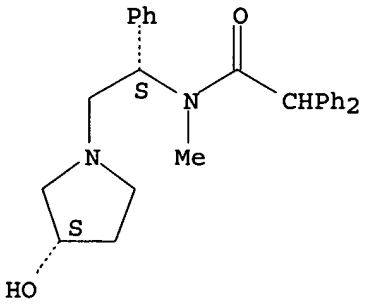
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10116978	A1	20021010	DE 2001-10116978	20010405
CA 2443019	AA	20021017	CA 2002-2443019	20020313
WO 2002080905	A1	20021017	WO 2002-EP2756	20020313
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
BR 2002008488	A	20040302	BR 2002-8488	20020313
EP 1397128	A1	20040317	EP 2002-724228	20020313
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1499967	A	20040526	CN 2002-807398	20020313
JP 2004525165	T2	20040819	JP 2002-578944	20020313
US 2004157913	A1	20040812	US 2003-474312	20031007
ZA 2003008600	A	20040913	ZA 2003-8600	20031104
PRIORITY APPLN. INFO.:			DE 2001-10116978 A	20010405

Young, Shawquia

WO 2002-EP2756 W 20020313

IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kappa opiate agonist asimadoline for treatment of bladder diseases especially irritable bladder syndrome)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 23 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 14 Nov 2001
AB The authors have previously found that the κ-opioid agonist, Asimadoline, attenuates adjuvant arthritis in a dose-dependent, antagonist-reversible manner. To elucidate possible mechanisms, the authors investigated the effects of Asimadoline (5 mg/kg/day i.p.) or vehicle on in vivo cytokine expression and T-cell recruitment in adjuvant arthritis. Arthritis severity was assessed every 3-4 days for 21 days. Rats were killed on days 0, 13, and 21 post-induction and synovial membrane and inguinal lymph nodes were removed for mRNA extraction Changes in cytokine mRNA expression were measured using reverse transcription-polymerase chain reaction (RT-PCR) and densitometry. T cells in joints were quantified by immunohistochem. Asimadoline significantly decreased arthritis severity at day 13, with a concomitant decrease in synovial membrane expression of cytokines interleukin 17 and transforming growth factor-β (TGF-β) mRNA at day 13, and no change in T cell nos. in the joints of arthritic rats. By contrast, in the inguinal lymph nodes, expression of tumor necrosis factor was increased at day 13 and TGF-β mRNA was increased throughout. An altered balance, therefore, in the pro- and anti-inflammatory effects of TGF-β by Asimadoline might explain its striking anti-arthritic actions.

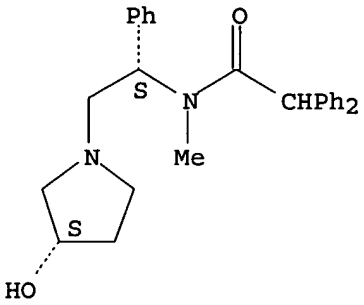
ACCESSION NUMBER: 2001:824779 HCAPLUS
DOCUMENT NUMBER: 137:41407
TITLE: The κ-opioid agonist, Asimadoline, alters cytokine gene expression in adjuvant arthritis
AUTHOR(S): Bush, K. A.; Kirkham, B. W.; Walker, J. S.
CORPORATE SOURCE: School of Physiology and Pharmacology, University of New South Wales, Sydney, 2052, Australia
SOURCE: Rheumatology (Oxford, United Kingdom) (2001), 40(9), 1013-1021
CODEN: RUMAFK; ISSN: 1462-0324
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

Young, Shawquia

08/06/2006

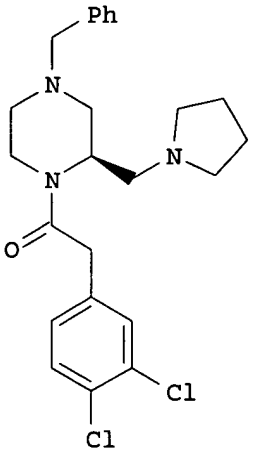
IT **153205-46-0**, Asimadoline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Asimadoline alters cytokine gene expression in adjuvant arthritis)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 17 Oct 2001
GI



I

AB Title compds., e.g., I, were prepared Data for biol. activity of title compds. were given.
ACCESSION NUMBER: 2001:757813 HCAPLUS
DOCUMENT NUMBER: 135:318517
TITLE: Preparation of 1-aralkanoyl-2-pyrrolidinomethylpiperazines and analogs as κ-opioid receptor agonists
INVENTOR(S): Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael

Young, Shawquia

	Anthony; Kumar, Virendra; Gaul, Forrest; Chang, An-Chih; Guo, Deqi
PATENT ASSIGNEE(S):	Adolor Corporation, USA
SOURCE:	U.S., 115 pp., Cont.-in-part of U.S. 5,945,443. CODEN: USXXAM
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	8
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6303611	B1	20011016	US 1998-150369	19980909
US 5646151	A	19970708	US 1996-612680	19960308
US 5688955	A	19971118	US 1997-796078	19970205
US 5744458	A	19980428	US 1997-899086	19970723
US 5945443	A	19990831	US 1998-34661	19980303
US 6057323	A	20000502	US 1998-183011	19981030
US 6054445	A	20000425	US 1999-307387	19990507
CA 2342994	AA	20000316	CA 1999-2342994	19990616
WO 2000014065	A1	20000316	WO 1999-US13680	19990616
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9944428	A1	20000327	AU 1999-44428	19990616
AU 746422	B2	20020502		
EP 1112252	A1	20010704	EP 1999-927550	19990616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002524444	T2	20020806	JP 2000-568824	19990616
NZ 510058	A	20030829	NZ 1999-510058	19990616
US 6239154	B1	20010529	US 1999-372191	19990811
US 6391910	B1	20020521	US 2000-478482	20000106
US 2002013296	A1	20020131	US 2001-803957	20010313
US 6486165	B2	20021126		
US 2002103164	A1	20020801	US 2001-803976	20010313
US 6476063	B2	20021105		
US 6492351	B1	20021210	US 2001-803901	20010313
US 2003144272	A1	20030731	US 2002-146693	20020515
US 6750216	B2	20040615		
US 2005020576	A1	20050127	US 2004-807113	20040323

PRIORITY APPLN. INFO.:	US 1996-612680	A1 19960308
	US 1997-796078	A3 19970205
	US 1997-899086	A3 19970723
	US 1998-34661	A2 19980303
	US 1998-150369	A2 19980909
	US 1998-183011	A3 19981030
	WO 1999-US13680	W 19990616
	US 1999-372191	A3 19990811
	US 2000-478482	A2 20000106
	US 2002-146693	A1 20020515

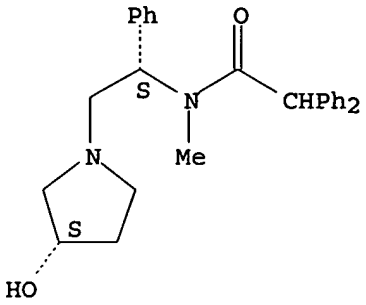
IT **185951-07-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 1-aralkanoyl-2-pyrrolidinomethylpiperazines and analogs as κ-opioid receptor agonists)

Young, Shawquia

08/06/2006

RN 185951-07-9 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 03 Aug 2001
AB Norepinephrine (NE) reduces the release of neuropeptides from central terminals of primary afferent neurons by presynaptic inhibition. The authors investigated whether NE also affects stimulus-induced intracutaneous calcitonin gene-related peptide (CGRP) and secondary prostaglandin E2 (PGE2) release. For comparison, κ-opioid effects were examined Antidromic elec. nerve stimulation resulted in significant increases in the release of CGRP and PGE2. The PGE2 release was prevented by selective activation of α2-adrenoceptors, whereas the CGRP release was not changed. In contrast, selective κ-opioid receptor activation diminished elec. evoked release of both CGRP and PGE2. The authors conclude that NE affected stimulated PGE2 release via α2-adrenoceptors on cells other than cutaneous afferents while κ-opioid receptors are expressed in peripheral terminals of cutaneous afferents and their activation reduced CGRP release and secondary PGE2 formation.
ACCESSION NUMBER: 2001:563491 HCAPLUS
DOCUMENT NUMBER: 135:283446
TITLE: Modulation of CGRP and PGE2 release from isolated rat skin by α-adrenoceptors and κ-opioid-receptors
AUTHOR(S): Averbeck, B.; Reeh, P. W.; Michaelis, M.
CORPORATE SOURCE: Department of Physiology and Experimental Pathophysiology, University of Erlangen-Nurnberg, Erlangen, D-91054, Germany
SOURCE: NeuroReport (2001), 12(10), 2097-2100
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

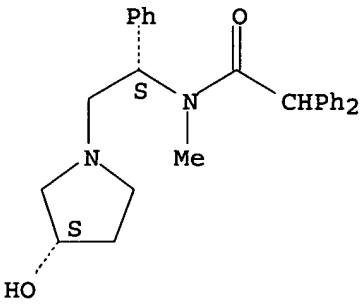
Young, Shawquia

(norepinephrine modulation of CGRP and PGE2 release from isolated rat skin by α-adrenoceptors and κ-opioid-receptors)

RN 153205-46-0 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ED Entered STN: 05 Apr 2001

AB Squirrel monkeys were trained to discriminate i.m. injections of the κ-opioid receptor agonist enadoline (0.0017 mg/kg) from saline in a two-lever drug-discrimination procedure. Enadoline produced a reliable discriminative stimulus that was reproduced by the κ-selective agonists PD 117302, U 50,488, GR 89686A, (-)-spiradoline, ICI 204448, and EMD 61753, and by the mixed-action κ/μ-agonists bremazocine and ethylketocyclazocine. The discriminative stimulus effects of enadoline were not reproduced by the μ-selective agonist morphine, the δ-selective agonist BW373U86, the mixed-action opioids nalbuphine and nalorphine, or by the less active enantiomers of enadoline and spiradoline PD 129829 and (+)-spiradoline, resp. The selective μ-opioid antagonist β-funaltrexamine (10.0.mg/kg) did not appreciably alter the dose-effect function for enadoline in any subject. However, the nonselective and κ-selective opioid antagonists quadazocine (0.03-3.0 mg/kg) and nor-BNI (3-10 mg/kg), and the mixed-action opioid nalbuphine (0.3-30 mg/kg) served to surmountably antagonize enadoline's discriminative stimulus effects. The antagonist effects of nor-BNI were long-lasting and did not distinguish between drugs purported to act at different κ-receptor subtypes. The present results bolster the view that common discriminative stimulus effects of enadoline and other opioids are mediated by κ-agonist actions that are surmountably antagonized by nor-BNI in a long-lasting manner. The enadoline-antagonist effects of nalbuphine support the idea that it acts with low efficacy at κ-opioid receptors.

ACCESSION NUMBER: 2001:240832 HCAPLUS

DOCUMENT NUMBER: 135:117110

TITLE: Enadoline discrimination in squirrel monkeys: effects of opioid agonists and antagonists

AUTHOR(S): Carey, Galen J.; Bergman, Jack

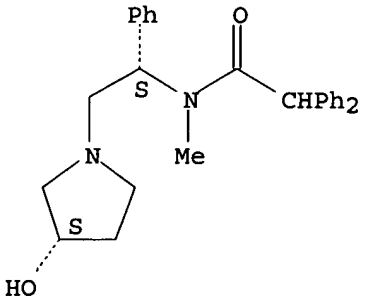
CORPORATE SOURCE: Schering-Plough Research Institute, Kenilworth, NJ, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics (2001), 297(1), 215-223
CODEN: JPETAB; ISSN: 0022-3565

08/06/2006

PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(enadoline discrimination in squirrel monkeys: effects of opioid agonists and antagonists)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 09 Mar 2001
AB Topical or intranasal compns. and methods for treating otic pain caused by otitis, surgery, or swimmer's ear are disclosed. In particular, the invention discloses compns. and methods of using κ-opioid agonists locally for the prevention or alleviation of otic pain. Compns. also comprise antimicrobial, antiallergy, and anti-inflammatory agents to treat otic infections, allergies, and inflammations associated with otic pain. For example, an otic/nasal solution contained (by weight) a κ-opioid EMD-61753 0.01-1.0%, phosphate buffered saline 1.0%, Polysorbate 80 0.5%, and water up to 100%.
ACCESSION NUMBER: 2001:167792 HCAPLUS
DOCUMENT NUMBER: 134:227363
TITLE: Topical use of kappa opioid agonists to treat otic pain
INVENTOR(S): Gamache, Daniel A.; Yanni, John M.
PATENT ASSIGNEE(S): Alcon Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

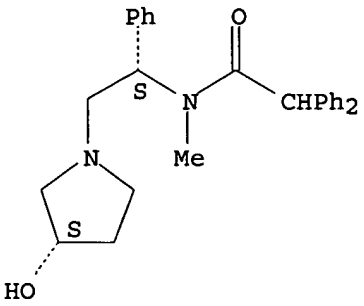
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001015678	A2	20010308	WO 2000-US22766	20000818
WO 2001015678	A3	20020103		

W: AU, BR, CA, CN, JP, MX, PL, TR, ZA

Young, Shawquia

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRIORITY APPLN. INFO.: US 1999-387359 A 19990831
IT **153205-46-0**, EMD-61753
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (topical compns. containing κ-opioid agonists for treatment of otic pain)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

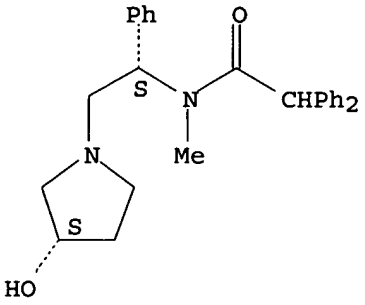


L4 ANSWER 28 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 06 Nov 2000
AB We have previously shown that the κ-opioid agonist, asimadoline, produces time-dependent changes in neuropeptide concns. in the joints of rats with chronic arthritis. We hypothesized that asimadoline acts on peripheral terminals to modulate substance P (SP) release. To address this hypothesis, here we have examined neuropeptide expression in their source cells in dorsal root ganglia (DRG) that innervate the joint, as well as in non-neuronal tissue, after treatment with asimadoline. We found an increased production of SP and CGRP in untreated chronic arthritic animals which supports our previous finding of increased SP content in the joint. More importantly, the κ-opioid asimadoline reduced the expression of both SP and calcitonin gene-related peptide-α (α-CGRP) in DRG cells but had no effect on the very low expression of neuropeptides in non-neuronal tissue. The fact that SP synthesis is attenuated by asimadoline accords with our hypothesis that the increased tissue levels of SP result from κ-mediated presynaptic inhibition of release leading to augmented tissue stores. These in vivo data confirm literature findings that opioids inhibit SP release from peripheral endings of primary afferent fibers.
ACCESSION NUMBER: 2000:775953 HCAPLUS
DOCUMENT NUMBER: 134:65944
TITLE: Effects of the peripherally selective κ-opioid asimadoline, on substance P and CGRP mRNA expression in chronic arthritis of the rat
AUTHOR(S): Walker, J. S.; Scott, C.; Bush, K. A.; Kirkham, B. W.
CORPORATE SOURCE: School of Physiology and Pharmacology, University of New South Wales, Sydney, 2052, Australia
SOURCE: Neuropeptides (Edinburgh) (2000), 34(3&4), 193-202
CODEN: NRPPDD; ISSN: 0143-4179
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

08/06/2006

IT **153205-46-0**, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of peripherally selective κ-opioid asimadoline, on substance P and CGRP mRNA expression in chronic arthritis of rat)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

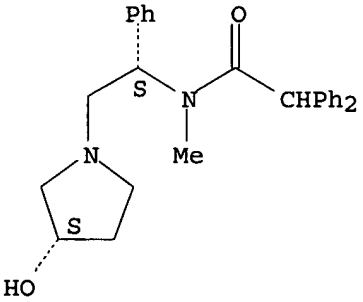
L4 ANSWER 29 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 15 Oct 2000
AB The effects were investigated of asimadoline, a new κ-opioid agonist, on renal function and on hormones related to body fluid balance as well as its tolerability in healthy subjects. In a placebo-controlled, randomized, double-blind crossover design the authors studied the effects of single oral doses of 1, 5, and 10 mg of asimadoline, in 24 healthy volunteers. 2 H control urine collections were followed by 2 h postdose urine collections and subsequently 2.5% saline was given i.v. at a rate of 0.3 mL min-1 kg-1 during another 2 h urine collection. Blood was obtained hourly. Arg-vasopressin (AVP), atrial natriuretic peptide (α-hANP), endothelin (ET-1), and cAMP were determined by RIA or ELISA. GC-MS measurements revealed Cmax values of asimadoline in plasma ranging from 18 ng ml-1 at the 1 mg dose, 91 ng ml-1 at the 5 mg dose, to 214 ng ml-1 at the 10 mg dose after an average of 1.1-1.4 h. Without effects on blood pressure, heart rate, GFR, or urine electrolyte excretion, urine volume increased after 1-2 h after administration of 5 and 10 mg asimadoline from 3.3 to 5.6 and from 3.2 to 5.5 mL min-1, resp. CH2O rose from 0.2 to 2.0 and from 0.6 mL min-1. Urinary excretion of AVP was suppressed only with the 10 mg dose from 46 to 25 fmol min-1 without and from 410 to 181 fmol min-1 with stimulation by 2.5% saline. Plasma AVP was suppressed only by the 10 mg dose of asimadoline in 6 of 8 subjects during the 2.5% saline infusion. Changes in the α-hANP or ET-1 systems were not affected by asimadoline. Asimadoline is diuretic in man after single doses of 5 or 10 mg probably through a direct effect at the renal tubular level. Suppression of AVP secretion was observed only at the highest dose level of 10 mg of asimadoline.
ACCESSION NUMBER: 2000:726377 HCAPLUS
DOCUMENT NUMBER: 134:247046
TITLE: Influence of asimadoline, a new κ-opioid receptor agonist, on tubular water absorption and vasopressin secretion in man

Young, Shawquia

AUTHOR(S): Kramer, H. J.; Uhl, W.; Ladstetter, B.; Backer, A.
CORPORATE SOURCE: Renal Section, Medical Policlinic, University of Bonn, Bonn, 53111, Germany
SOURCE: British Journal of Clinical Pharmacology (2000), 50(3), 227-235
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(asimadoline on tubular water absorption and vasopressin secretion)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



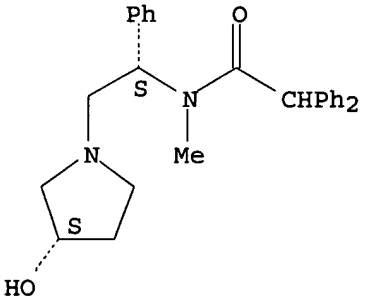
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 30 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 02 Aug 2000
AB κ-Opioid receptor agonists (κ-ORAs) have been shown to modulate visceral nociception through an interaction with a peripheral, possibly novel, κ-opioid-like receptor. We used in the present expts. an antisense strategy to further explore the hypothesis that κ-ORA effects in the colon are produced at a site different from the cloned κ-opioid receptor (KOR). An antisense oligodeoxynucleotide (ODN) to the cloned rat KOR was administered intrathecally (12.5 μg, twice daily for 4 d) to specifically knock-down the cloned KOR. Efficacy of the KOR antisense ODN treatment was behaviorally evaluated by assessing the antinociceptive effects of peripherally administered κ- (EMD 61,753 and U 69,593), μ- (DAMGO) and δ- (deltorphin) ORAs in the formalin test. Intrathecal antisense, but not mismatch ODN blocked the actions of EMD 61,753 and U 69,593 without affecting the actions of DAMGO or deltorphin; a complete recovery of antinociceptive actions of the κ-ORA EMD 61,753 was observed 10 d after the termination of antisense ODN treatment. In contrast, the ability of EMD 61,753 to dose-dependently attenuate responses of pelvic nerve afferent fibers to noxious colonic distension was unaffected in the same rats in which the antisense ODN effectively knocked-down the KOR as assessed in the formalin test. Addnl., Western blot anal. demonstrated a significant downregulation of KOR protein in the L4-S1 dorsal root ganglia of antisense, but not

mismatch ODN-treated rats. The present results support the existence of a non-κ-opioid receptor site of action localized in the colon.

ACCESSION NUMBER: 2000:525698 HCAPLUS
DOCUMENT NUMBER: 133:217585
TITLE: κ-opioid receptor agonists modulate visceral nociception at a novel, peripheral site of action
AUTHOR(S): Joshi, S. K.; Su, Xin; Porreca, Frank; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Neuroscience (2000), 20(15), 5874-5879
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(κ-opioid receptor agonists modulate visceral nociception at novel, peripheral site of action)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



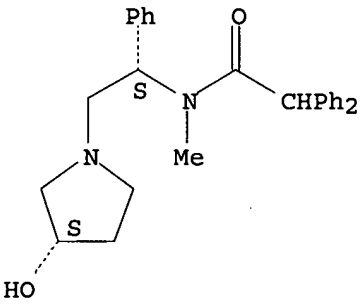
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 31 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 16 May 2000
AB Predicting blood-brain barrier (BBB) permeation remains a challenge in drug design. Since it is impossible to determine exptl. the BBB partitioning of large nos. of preclin. candidates, alternative evaluation methods based on computerized models are desirable. The present study was conducted to demonstrate the value of descriptors derived from 3D mol. fields in estimating the BBB permeation of a large set of compds. and to produce a simple math. model suitable for external prediction. The method used (VolSurf) transforms 3D fields into descriptors and correlates them to the exptl. permeation by a discriminant partial least squares procedure. The model obtained here correctly predicts more than 90% of the BBB permeation data. By quantifying the favorable and unfavorable contributions of physicochem. and structural properties, it also offers valuable insights for drug design, pharmacol. profiling, and screening. The computational procedure is fully automated and quite fast. The method thus appears as a valuable new tool in virtual screening where selection or prioritization of candidates is required from large collections of compds.
ACCESSION NUMBER: 2000:316267 HCAPLUS

08/06/2006

DOCUMENT NUMBER: 133:114594
TITLE: Predicting blood-brain barrier permeation from three-dimensional molecular structure
AUTHOR(S): Crivori, Patrizia; Cruciani, Gabriele; Carrupt, Pierre-Alain; Testa, Bernard
CORPORATE SOURCE: Institute of Medicinal Chemistry, University of Lausanne, Lausanne-Dorigny, CH-1015, Switz.
SOURCE: Journal of Medicinal Chemistry (2000), 43(11), 2204-2216
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(blood-brain barrier permeation prediction from 3D mol. structure)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 05 May 2000
AB Single-fiber recordings were made from the decentralized right cervical vagus nerve (hyponodosal) of the rat. A total of 56 afferent fibers that responded to gastric distension (GD) were studied: 6 fibers were stimulated by phasic balloon GD, 50 by fluid GD. All fibers gave increasing responses to increasing pressures of GD (5-60 mmHg). The effects of μ-opioid (morphine), δ-opioid (SNC80), and κ-opioid (EMD61,753, U62,066) receptor agonists were tested on responses of afferent fibers to GD. Morphine, administered systemically over a broad dose range (10 μg to 31 mg/kg, cumulative), had no effect on either resting activity or responses of vagal afferent fibers to GD. Similarly, the δ-opioid receptor agonist SNC80 (0.05-3.2 mg/kg) did not affect resting activity or responses to GD. In contrast, cumulative intra-arterial doses of the κ-opioid receptor agonist EMD61,753 or U62,066 dose dependently attenuated afferent fiber responses to GD. Doses producing inhibition to 50% of the control response to GD of EMD61,753 (8.0 mg/kg) and U62,066 (8.8 mg/kg) did not differ. The effect of U62,066 was moderately attenuated by a nonselective dose (4 mg/kg) of naloxone hydrochloride; the κ-opioid receptor-selective antagonist nor-BNI

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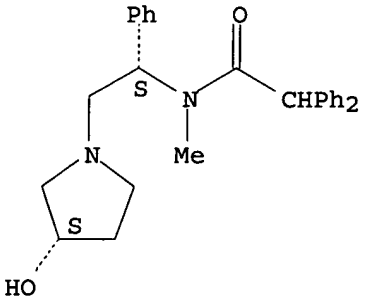
(20 mg/kg) was ineffective. These results demonstrate that κ-, but not μ- or δ-opioid receptor agonists modulate visceral sensation conveyed by vagal afferent fibers innervating the stomach. Given that κ-opioid receptor agonists effects were only modestly antagonized by naloxone and not at all by nor-BNI, the results point to a novel site of action.

ACCESSION NUMBER: 2000:292024 HCAPLUS
DOCUMENT NUMBER: 133:187887
TITLE: Differential effects of μ-, δ-, and κ-opioid receptor agonists on mechanosensitive gastric vagal afferent fibers in the rat
AUTHOR(S): Ozaki, Noriyuki; Sengupta, J. N.; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, University of Iowa, Iowa, IA, 52242, USA
SOURCE: Journal of Neurophysiology (2000), 83(4), 2209-2216
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **153205-46-0**, EMD61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential effects of μ-, δ-, and κ-opioid receptor agonists on mechanosensitive gastric vagal afferent fibers)

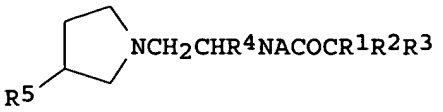
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

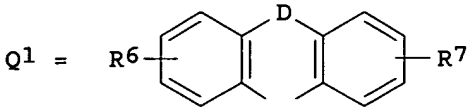


REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 04 May 2000
GI



I



AB Title compds. [I; R1 = Ar, cycloalkyl, cycloalkylalkyl; R2 = Ar; R1R2 = Q1; R3 = H, OH, OA, A; R4 = A, (substituted) Ph; R6, R7 = H, halo, OH, OA, CF3, NH2, NHA, NA2, NHCOA, NHCONH2, NO2, methylenedioxy; A = alkyl; Ar = mono- or bicyclic (substituted) (hetero)aryl; D = CH2, O, S, NH, NA, CH2CH2, CH:CH, CH2NH, CH2NA, bond], were prepared for the treatment of irritable bowel syndrome (no data). Thus, diphenylacetyl chloride in THF was added to (2S)-2-N-carboxyethyl-2-phenylglycine N,N-[(3S)-3-hydroxytetramethylamide] in THF at 10-20° to give 73.2% N-methyl-N-[(1S)-1-phenyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]ethyl]-2,2-diphenylacetamide hydrochloride. Drug formulations containing the latter are given.

ACCESSION NUMBER: 2000:289113 HCAPLUS
DOCUMENT NUMBER: 132:293664
TITLE: Preparation of pyrrolidinylethylacetamides as kappa opiate agonists for the treatment of irritable bowel syndrome.
INVENTOR(S): Gottschlich, Rudolf; Barber, Andrew
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

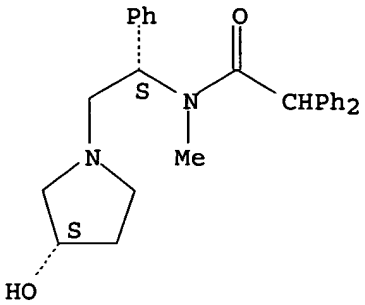
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19849650	A1	20000504	DE 1998-19849650	19981029

PRIORITY APPLN. INFO.: DE 1998-19849650 19981029
OTHER SOURCE(S): MARPAT 132:293664

IT **185951-07-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of pyrrolidinylethylacetamides as kappa opiate agonists for the treatment of irritable bowel syndrome)

RN 185951-07-9 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

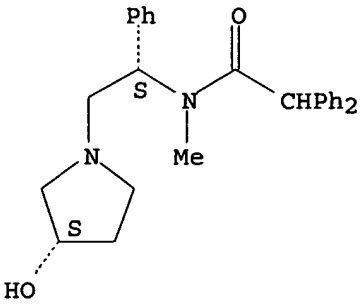
L4 ANSWER 34 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 01 Mar 2000
AB The authors studied the effects of intracolonic administration of opioid receptor agonists (ORAs) on responses of pelvic nerve afferent fibers to colorectal distension (CRD) and heat. Single-fiber recordings were made from the decentralized S1 dorsal rootlet in the rat. An .apprx.7-cm length of descending colon was isolated in situ to permit intracolonic perfusion with Krebs solution, which, when the outflow was clamped, was used to distend the colon. Responses to noxious CRD (40 mm Hg, 30 s) were tested after intracolonic instillation of μ-, δ-, or κ-ORAs. Intracolonic administration of the κ-ORAs EMD 61,753 (n = 5/12) and U62,066 (n = 8/11), but not either the μ-ORA fentanyl or the δ-ORA SNC-80, concentration-dependently inhibited responses of afferent fibers. For fibers unaffected by intracolonic administration of EMD 61,753 or U62,066, intra-arterial administration of κ-ORAs was effective. 41 Of 54 mechanosensitive fibers also responded to intracolonic instillation of heated Krebs solution (50°C). Intra-arterial injection of fentanyl or SNC-80 did not attenuate responses to heat. Either intracolonic or intra-arterial administration of EMD 61,753 or U62,066, however, inhibited afferent fiber responses to heat. These results document that mech. and thermal sensitivity of polymodal pelvic nerve afferent fibers innervating the rat colon can be inhibited peripherally by intracolonic instillation of κ-ORAs.

ACCESSION NUMBER: 2000:140109 HCAPLUS
DOCUMENT NUMBER: 133:12659
TITLE: Effects of intracolonic opioid receptor agonists on polymodal pelvic nerve afferent fibers in the rat
AUTHOR(S): Su, X.; Julia, V.; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, The University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Journal of Neurophysiology (2000), 83(2), 963-970
CODEN: JONEA4; ISSN: 0022-3077
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(intracolonic opioid receptor agonists on polymodal pelvic nerve afferent fibers, responses to colorectal distension and heat.)

08/06/2006

RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 09 Jan 2000
AB The higher incidence of inflammatory and painful disorders in women and recent reports that have emphasized the importance of gender in nociceptive sensitivity and responsiveness to analgesics prompted us to investigate gender as a factor in the variability in response to opioids. We studied the anti-inflammatory and antinociceptive effects of two κ-opioid agonists in adjuvant-induced arthritis, one that acts both peripherally and centrally (PNU50488H; 20 mg/kg/day), the other which is peripherally selective (asimadoline; 5 mg/kg/day). Both drugs had equally powerful anti-inflammatory effects in both male and female rats (reducing measures by 60-80%). In contrast, there were gender-based heterogeneities in their analgesic actions, contingent on the method of stimulation (mech. or thermal); males were insensitive to the analgesic effects of asimadoline with thermal but not mech. nociceptive stimuli. We also sought evidence for gender influences on the joint content of Substance P (SP), a peptide suggested to have a role in producing inflammation and found that levels were higher in the untreated arthritic females, although there were no gender differences in disease sensitivity or nociception in arthritic animals receiving no drugs. Paradoxically, both drugs elevated SP concns. in the joints, perhaps as a consequence of an action of κ-opioids to suppress SP release from peripheral nerves, but the gender differences remained. Further expts. are required to determine exact mechanisms responsible for the gender distinction in analgesic response to κ-opioids that may involve differential activation of primary afferents.

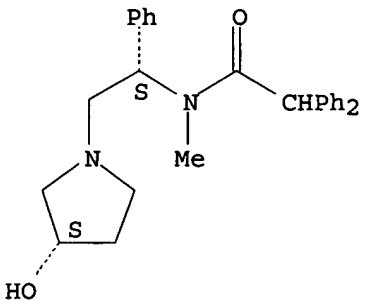
ACCESSION NUMBER: 2000:17577 HCAPLUS
DOCUMENT NUMBER: 132:189461
TITLE: Effect of gender on anti-inflammatory and analgesic actions of two κ-opioids
AUTHOR(S): Binder, Waltraud; Carmody, John; Walker, Judith
CORPORATE SOURCE: School of Physiology and Pharmacology, University of New South Wales, Sydney, Australia
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2000), 292(1), 303-309
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics

Young, Shawquia

08/06/2006

DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gender effect on κ-opioids antiinflammatory and analgesic action)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

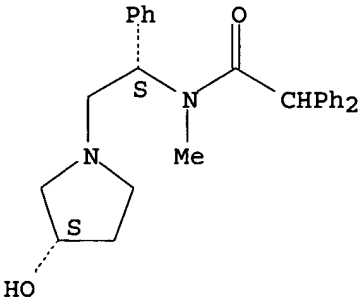
L4 ANSWER 36 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 18 Nov 1999
AB Paw-pressure vocalization thresholds were used to study the antinociceptive effect of the peripherally selective κ-opioid agonist asimadoline in both morphine-tolerant and opioid-naive rats 2 wk after chronic constriction injury (CCI) of the sciatic nerve. In naive rats, intraplantar injection of asimadoline into the nerve-injured paw, at doses of 10, 15 and 20 (but not 30) μg, dose-dependently relieved the mech. allodynia-like behavior. The κ-opioid antagonist norbinaltorphimine, (30 μg, intraplantar) reversed this action; injection of asimadoline (15 μg) into the contralateral paw (intraplantar or i.v.), however, had no effect. These results confirm that at low doses, asimadoline exerts its action only in the periphery. In morphine-tolerant rats (after 10 mg/kg s.c., twice daily for 4 days) and naive, saline-pretreated rats, asimadoline (15 μg, intraplantar) relieved the mech. allodynia-like behavior to the same extent, indicating no cross-tolerance between morphine and the peripherally selective drug. The findings show promise for the treatment of neuropathic pain with low doses of peripherally selective κ-opioids.
ACCESSION NUMBER: 1999:733604 HCAPLUS
DOCUMENT NUMBER: 132:303293
TITLE: Lack of cross-tolerance between the antinociceptive effects of systemic morphine and asimadoline, a peripherally selective κ-opioid agonist, in CCI-neuropathic rats
AUTHOR(S): Walker, J.; Catheline, G.; Guilbaud, G.; Kayser, V.
CORPORATE SOURCE: School of Physiology & Pharmacology, University of New South Wales, Sydney, Australia
SOURCE: Pain (1999), 83(3), 509-516
CODEN: PAINDB; ISSN: 0304-3959

Young, Shawquia

08/06/2006

PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(lack of cross-tolerance between the antinociceptive effects of systemic morphine and asimadoline, a κ-opioid agonist, in neuropathic pain)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 37 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 08 Jul 1999
AB Composition of matter for application to a body surface or membrane to administer asimadoline by permeation through the body surface or membrane, the composition comprising asimadoline (I) to be administered, at a therapeutically effective rate, alone or in combination with a permeation enhancer or mixture Also disclosed are drug delivery devices and methods for the transdermal administration of I. Drug reservoir were prepared by mixing I-HCl, EVA and dodecyl acetate, glycerol monolaurate, PVP, dimethyllauramide, and/or caproyllactylic acid. The resulting mix was then calendered to a 5 mil thickness between 2 release liners. The drug reservoir was then heat laminated to a Medpar backing.
ACCESSION NUMBER: 1999:421558 HCAPLUS
DOCUMENT NUMBER: 131:63445
TITLE: Novel formulations for the transdermal administration of asimadoline
INVENTOR(S): Van Osdol, William; Watanabe, Tyler
PATENT ASSIGNEE(S): Alza Corporation, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

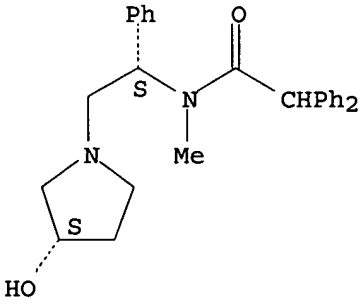
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932096	A1	19990701	WO 1998-US26652	19981215
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,				

DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9918283	A1	19990712	AU 1999-18283		19981215
US 2001051181	A1	20011213	US 1998-213478		19981217
PRIORITY APPLN. INFO.:			US 1997-68376P	P	19971222
			WO 1998-US26652	W	19981215

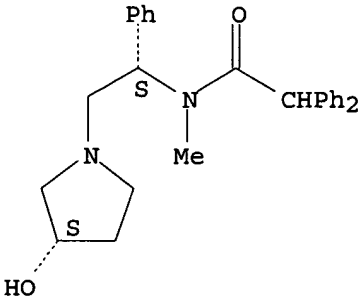
IT **153205-46-0**, Asimadoline **185951-07-9**, Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride
RL: BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(transdermal asimadoline formulations)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 185951-07-9 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

08/06/2006

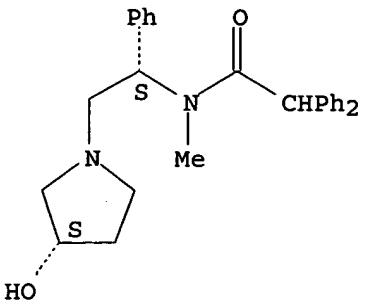
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 07 Jul 1999
AB The objective of the present study was to evaluate the effects of EMD 61753 (asimadoline), a κ-opioid receptor agonist with restricted access to the central nervous system, on postoperative pain in patients who underwent knee surgery and on nociceptive thresholds and inflammation in rats treated with Freund's complete adjuvant. Patients treated with EMD 61753 (10 mg p.o.) tended to report an increase in pain, as evaluated by a visual analog scale and by the time to the first request for and the total amount of supplemental analgesic medication. The global tolerability of EMD 61753 was assessed as significantly inferior to that of a placebo by the investigator. In rats, the bilateral intraplantar (i.pl.) injection of EMD 61753 (0.1-3.2 mg) resulted in dose-dependent antinociception in both inflamed and noninflamed paws, with a peak at 5 min after injection, as evaluated by the paw pressure method. However, at later time points (1 h-4 days), a significant decrease in the paw pressure threshold was observed, confirming its tendency toward a hyperalgesic action in humans. This was accompanied by an increase in paw volume and paw temperature, with a peak at 6 h after injection. EMD 61753 (1.6 mg)-induced analgesia was blocked by the peripheral opioid receptor antagonist naloxone methiodide (2.5-10 mg/kg s.c.) and by the κ receptor antagonist nor-binaltorphimine (0.1 mg; i.pl.). In contrast, EMD 61753 (1.6 mg)-induced hyperalgesia and increases in paw volume and paw temperature were blocked neither by naloxone methiodide (10-40 mg/kg s.c.) nor by dizocilpine maleate (0.003-0.009 mg i.pl.), a N-methyl-D-aspartic acid receptor antagonist. These data show differentially mediated peripheral actions of EMD 61753: κ-opioid receptor-induced analgesia and nonopioid, non-N-methyl-D-aspartic acid hyperalgesic and proinflammatory effects.

ACCESSION NUMBER: 1999:416145 HCAPLUS
DOCUMENT NUMBER: 131:179631
TITLE: Peripheral effects of the κ-opioid agonist EMD 61753 on pain and inflammation in rats and humans
AUTHOR(S): Machelska, Halina; Pfluger, Martina; Weber, Werner; Piranvisseh-Volk, Mojgan; Daubert, Jeffrey D.; Dehaven, Robert; Stein, Christoph
CORPORATE SOURCE: Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1999), 290(1), 354-361
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peripheral effects of the κ-opioid agonist EMD 61753 on pain and inflammation in rats and humans)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Young, Shawquia



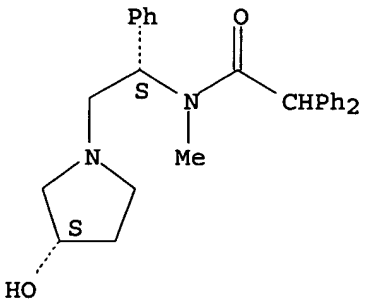
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 39 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 19 May 1999
AB Studies with knockout mice lacking mdr 1a P-glycoprotein (P-gp) have previously shown that blood-brain barrier P-gp is important in preventing the accumulation of several drugs in the brain. Asimadoline (EMD 61753) is a peripherally selective κ-opioid receptor agonist which is under development as a therapeutic analgesic. From the structural characteristics of this drug and its peripheral selectivity, we hypothesized that it is transported by P-gp. Using a pig-kidney polarized epithelial cell line transfected with mdr cDNAs, we demonstrate that asimadoline is transported by the mouse mdr 1a P-gp and the human MDR1 P-gp. Furthermore, we show that in mdr 1a/1b double knockout mice, the absence of P-gp leads to a 9 fold increased accumulation of asimadoline in the brain. In line with this accumulation difference, mdr 1a/1b (-/-) mice are at least 8 fold more sensitive to the sedative effect of asimadoline than wild-type mice. Interestingly, the oral uptake of asimadoline was not substantially altered in mdr 1a/1b (-/-) mice. Our results demonstrate that for some drugs, P-gp in the blood-brain barrier can have a therapeutically beneficial effect by limiting brain penetration, whereas at the same time intestinal P-gp is not a significant impediment to oral uptake of the drug.
ACCESSION NUMBER: 1999:305633 HCAPLUS
DOCUMENT NUMBER: 131:96939
TITLE: Role of blood-brain barrier P-glycoprotein in limiting brain accumulation and sedative side-effects of asimadoline, a peripherally acting analgesic drug
AUTHOR(S): Jonker, J. W.; Wagenaar, E.; Van Deemter, L.; Gottschlich, R.; Bender, H. M.; Dasenbrock, J.; Schinkel, A. H.
CORPORATE SOURCE: Division of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, 1066 CX, Neth.
SOURCE: British Journal of Pharmacology (1999), 127(1), 43-50
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(role of blood-brain barrier P-glycoprotein in limiting brain accumulation and sedative side-effects of asimadoline)
RN 153205-46-0 HCAPLUS

08/06/2006

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



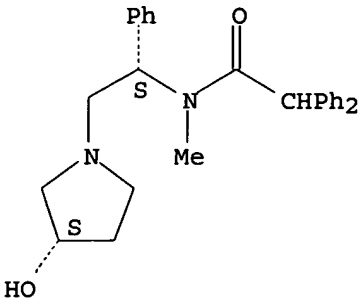
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 24 Dec 1998
AB The objective of this study was to examine the antinociceptive effects of peripherally restricted κ-opioid receptor agonists (ORAs) in a rat model of inflammatory bowel disease produced by intracolonic instillation of trinitrobenzine sulfonic acid (TNBS). Antinociceptive effects of μ-(morphine) and κ-ORAs (EMD 61753 and ICI 204488) were evaluated in a behavioral model of visceral nociception. The effects of these agonists and a δ-ORA (SNC 80) on responses of pelvic nerve afferent fibers innervating the colon were also tested. In the behavioral study, systemic injections of morphine and both κ-ORAs dose-dependently inhibited the visceromotor response to colorectal distension in rats with uninflamed or inflamed colons. The inhibitory effects of κ-ORAs, but not morphine, were significantly greater in rats with colons inflamed 4 days previously by TNBS. A μ-receptor-selective dose (30 μg/kg) of naloxone methiodide (NLXM) blocked the inhibitory effect of morphine, but not of EMD 61 753. In the single-fiber study, neither morphine nor the δ-ORA SNC 80 attenuated the responses of pelvic nerve afferent fibers, whereas κ-ORAs dose-dependently inhibited responses of pelvic nerve afferent fibers with significantly greater potency in the inflamed colon. Pretreatment with a non-opioid receptor-selective dose (2 mg/kg) of NLXM produced a rightward shift in the dose-response function of EMD 61 753. The greater potency of κ-ORAs in the TNBS-inflamed condition suggests a peripheral upregulation of κ-opioid receptors in colonic inflammation.
ACCESSION NUMBER: 1998:806223 HCAPLUS
DOCUMENT NUMBER: 131:27793
TITLE: Effects of kappa opioids in the inflamed rat colon
AUTHOR(S): Sengupta, J. N.; Snider, Anne; Su, Xin; Gebhart, G. F.
CORPORATE SOURCE: College of Medicine, Department of Pharmacology, The University of Iowa, Iowa City, IA, 52242, USA
SOURCE: Pain (1999), 79(2,3), 175-185
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

Young, Shawquia

(effects of kappa opioids in the inflamed rat colon)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

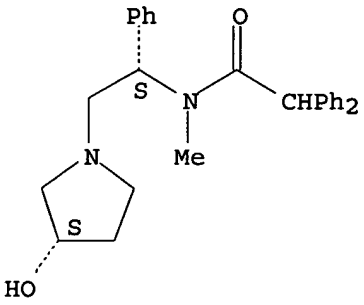


L4 ANSWER 41 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 19 Oct 1998
AB Fifty-three compds. with clin. established ability to cross or not to cross the blood-brain barrier by passive diffusion were characterized by means of surface activity measurements in terms of three parameters, i.e., the air-water partition coefficient, Kaw, the critical micelle concentration, CMCD, and the cross-sectional area, AD. A three-dimensional plot in which the surface area, AD, is plotted as a function of Kaw-1 and CMCD shows essentially three groups of compds.: (i) very hydrophobic compds. with large air-water partition coeffs. and large cross-sectional areas, AD > 80 Å2, which do not cross the blood-brain barrier, (ii) compds. with lower air-water partition coeffs. and an average cross-sectional area, AD .simeq. 50 Å2, which easily cross the blood-brain barrier, and (iii) hydrophilic compds. with low air-water partition coeffs. (AD < 50 Å2) which cross the blood-brain barrier only if applied at high concns. It was shown that the lipid membrane-water partition coefficient, Klw, measured previously, can be correlated with the air-water partition coefficient if the addnl. work against the internal lateral bilayer pressure, πbi = 34 ± 4 mN/m, is taken into account. The partitioning into anisotropic lipid membranes decreases exponentially with increasing cross-sectional areas, AD, according to Klw = constant Kaw exp(-ADπbi/kT), where kT is the thermal energy. The cross-sectional area of the mol. oriented at a hydrophilic-hydrophobic interface is thus the main determinant for membrane permeation provided the mol. is surface active and has a pKa > 4 for acids and a pKa < 10 for bases.
ACCESSION NUMBER: 1998:657620 HCAPLUS
DOCUMENT NUMBER: 130:32678
TITLE: Blood-brain barrier permeation: molecular parameters governing passive diffusion
AUTHOR(S): Fischer, H.; Gottschlich, R.; Seelig, A.
CORPORATE SOURCE: Department of Biophysical Chemistry, Biocenter of the University of Basel, Basel, CH-4056, Switz.
SOURCE: Journal of Membrane Biology (1998), 165(3), 201-211
CODEN: JMBBBO; ISSN: 0022-2631
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, Asimadoline

Young, Shawquia

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(phys. chemical parameters governing passive diffusion of agents through blood-brain barrier)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 42 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 10 Jul 1998
AB Compns. and methods for treating ocular pain are disclosed. In particular, the invention discloses compns. and methods of using κ-opioid agonists topically for the prevention or alleviation of ocular pain, especially from photorefractive keratotomy. An ophthalmic composition contained EMD-61753 0.01-10, phosphate-buffered saline 1, Polysorbate-80 0.5, and purified water to 100 %.

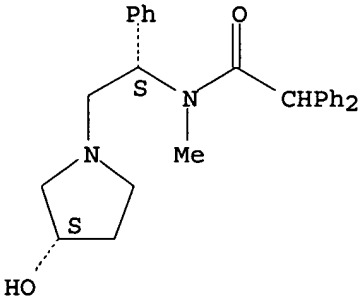
ACCESSION NUMBER: 1998:424114 HCAPLUS
DOCUMENT NUMBER: 129:100031
TITLE: The topical use of κ-opioid agonists to treat ocular pain
INVENTOR(S): Gamache, Daniel A.
PATENT ASSIGNEE(S): Alcon Laboratories, Inc., USA; Gamache, Daniel A.
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9826770	A2	19980625	WO 1997-US23185	19971211
WO 9826770	A3	19980903		
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2275167	AA	19980625	CA 1997-2275167	19971211
AU 9858987	A1	19980715	AU 1998-58987	19971211
AU 731447	B2	20010329		
EP 946157	A2	19991006	EP 1997-954571	19971211
EP 946157	B1	20020313		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

	IE, FI				
JP 2001506652	T2	20010522	JP 1998-527903		19971211
AT 214272	E	20020315	AT 1997-954571		19971211
ES 2174337	T3	20021101	ES 1997-954571		19971211
US 6191126	B1	20010220	US 1999-319064		19990527
HK 1020867	A1	20020830	HK 1999-105517		19991127
PRIORITY APPLN. INFO.:			US 1996-32909P	P	19961216
			WO 1997-US23185	W	19971211

IT **153205-46-0**, EMD-61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(topical use of κ-opioid agonists to treat ocular pain)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

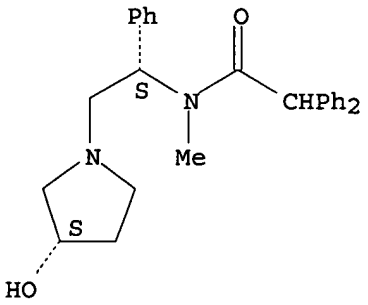


L4 ANSWER 43 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 08 Jul 1998
AB In a double-blind, cross-over study, ibuprofen (600 mg), a peripherally-acting selective κ-opioid receptor agonist (7.5 mg), or placebo were given orally in expts. on healthy volunteers 1 h before assessment of pain thresholds to radiant heat and of pain ratings to controlled mech. impact stimuli. Mech. and thermal hyperalgesia had been induced 24 h before by irradiating skin patches on the ventral side of the upper leg. UVB irradiation induced mech. and thermal hyperalgesia at radiation dosages of three times the minimal erythema dose. UVA irradiation resulted in an immediate erythema and a delayed tanning of the skin, however, no hyperalgesia was observed For comparison another model of mech. hyperalgesia was applied in the same expts. which has been previously proven sensitive to non-steroidal anti-inflammatory drugs (NSAIDs). In this model hyperalgesia was assessed, which develops during repetitive pinching of skin folds (pinch model). Ibuprofen significantly diminished heat and mech. hyperalgesia induced by UVB, but had no effect on pain responses obtained from untreated skin. It also had an antihyperalgesic effect in the pinch stimulus paradigm. In contrast, the κ-agonist showed no antihyperalgesic efficacy in the chosen models. It is concluded that the UVB model, as the pinch model, is suitable for establishing antihyperalgesic effects of NSAIDs, but probably not of κ-receptor agonists, in healthy human volunteers. Compared to the pinch stimulus model, the UVB model offers addnl. advantages: (a) drugs may be tested after induction of the skin trauma by UV and this situation is more similar to the clin. use of antihyperalgesic drugs. (b) Since mech. and thermal hyperalgesia is induced by UVB, drug effects can be tested upon

both forms of hyperalgesia.

ACCESSION NUMBER: 1998:416524 HCAPLUS
DOCUMENT NUMBER: 129:225416
TITLE: Effects of antihyperalgesic drugs on experimentally induced hyperalgesia in man
AUTHOR(S): Bickel, A.; Dorfs, S.; Schmelz, M.; Forster, C.; Uhl, W.; Handwerker, H. O.
CORPORATE SOURCE: Department of Physiology I, University of Erlangen/Nurnberg, Erlangen, 91054, Germany
SOURCE: Pain (1998), 76(3), 317-325
CODEN: PAINDB; ISSN: 0304-3959
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of antihyperalgesic drugs on exptl. induced hyperalgesia in man)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 44 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 08 Jul 1998
AB Opioids, though widely used as analgesics, have not been seriously considered as therapy for rheumatoid arthritis. The present study evaluated the dose-effect and time-dependence relationships of a new peripherally selective κ agonist, asimadoline, in rats with adjuvant arthritis. The arthritis was assessed by a pooled severity index combining the comprehensive criteria of edema, radiog. and histol. changes, in the hind limbs. Asimadoline was extremely effective in attenuating joint damage (by up to 80%) when administered parenterally (0.5 to 10 mg kg-1 day-1, i.p.) throughout the disease or during its early phase; treatment was less successful if confined to the latter stages. Ten fold higher doses were effective orally. Equimolar doses of a peripherally-selective antagonist, naloxone methiodide, and the κ-selective antagonist, MR2266, fully reversed the peripheral anti-arthritic effects of asimadoline (5 mg kg-1 day-1), indicating that asimadoline acts through peripheral κ-opioid receptors. However, an equivalent dose of MR2266 did not fully reverse the anti-arthritic effects of

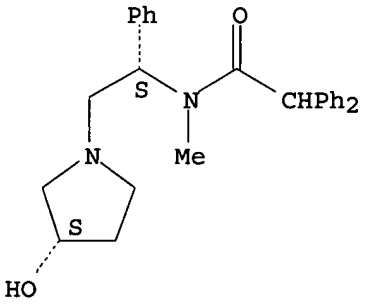
the highest dose of asimadoline (40 mg kg-1 day-1), suggesting a loss of κ-selectivity at this dose. Asimadoline also exhibited analgesic effects (mech. nociceptive thresholds) in arthritic but not non-arthritic rats, indicating that inflammation is necessary for asimadoline-induced analgesia. These data confirm our previous findings that κ-opioids possess anti-arthritic properties and that these effects are mediated via peripheral κ-receptors. The present results are new in showing that the peripherally acting κ-opioid agonist, asimadoline, is a potent anti-arthritic agent. Such novel drugs, essentially lacking central side effects, herald new treatments for rheumatoid arthritis.

ACCESSION NUMBER: 1998:413024 HCAPLUS
DOCUMENT NUMBER: 129:144659
TITLE: Effect of the peripherally selective κ-opioid agonist, asimadoline, on adjuvant arthritis
AUTHOR(S): Binder, Waltraud; Walker, Judith S.
CORPORATE SOURCE: School of Physiology and Pharmacology, University of New South Wales, Sydney, 2052, Australia
SOURCE: British Journal of Pharmacology (1998), 124(4), 647-654
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(κ-opioid agonist asimadoline effect on adjuvant arthritis)

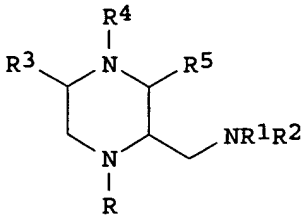
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 45 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 29 Jun 1998
GI



I

AB Title compds. [I; R = CO(CH2)nR6; R1,R2 = Me; R1R2 = (CH2)m, CH2CH(OH)CH2, CH2CH2OCH2CH2, etc.; R3,R5 = CH2NHSO2Me, CH2NHP(O)(OH)2, CH2OP(O)(OH)2, etc.; R4 = P(O)(OH)2, (CH2)pCO2H, CO2Me, etc.; R6 = (un)substituted (hetero)aryl; m = 4-8; n = 1-3; p = 0-20] were prepared for treatment of pruritus. Thus, (R)-I (R = COCH2C6H3Cl2-3,4, NR1R2 = pyrrolidino, R3 = R5 = H, R4 = SO2Me) was prepared Data for biol. activity of I were given.

ACCESSION NUMBER: 1998:397785 HCAPLUS
DOCUMENT NUMBER: 129:67799
TITLE: Preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as kappa opioid receptor agonists
INVENTOR(S): Kruse, Lawrence I.; Chang, An-Chih; DeHaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan
PATENT ASSIGNEE(S): Adolor Corp., USA
SOURCE: U.S., 67 pp., Cont.-in-part of U. S. 5,688,955.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5763445	A	19980609	US 1997-891833	19970714
US 5646151	A	19970708	US 1996-612680	19960308
US 5688955	A	19971118	US 1997-796078	19970205
US 5981513	A	19991109	US 1998-45522	19980321
CA 2289055	AA	19990128	CA 1998-2289055	19980619
WO 9903468	A1	19990128	WO 1998-US12769	19980619
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9879801	A1	19990210	AU 1998-79801	19980619
AU 725232	B2	20001012		
EP 998281	A1	20000510	EP 1998-930400	19980619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9810712	A	20000905	BR 1998-10712	19980619
JP 2001510154	T2	20010731	JP 2000-502767	19980619
NZ 513889	A	20010928	NZ 1998-513889	19980619
NZ 500439	A	20011026	NZ 1998-500439	19980619
ZA 9806208	A	19990125	ZA 1998-6208	19980713

Young, Shawquia

US 6028063	A	20000222	US 1999-307517	19990507
US 6180623	B1	20010130	US 1999-436057	19991108
NO 9906352	A	20000313	NO 1999-6352	19991220
US 2002042399	A1	20020411	US 2001-769450	20010126
US 2003236248	A1	20031225	US 2003-455545	20030605
US 2004220112	A1	20041104	US 2003-455687	20030605
US 6960612	B2	20051101		
NO 2005004249	A	20000313	NO 2005-4249	20050914

PRIORITY APPLN. INFO.:

US 1996-612680	A2	19960308
US 1997-796078	A2	19970205
US 1997-891833	A3	19970714
US 1998-45522	A3	19980321
WO 1998-US12769	W	19980619
US 1999-307517	A3	19990507
US 1999-436057	A1	19991108
US 2001-769450	A3	20010126

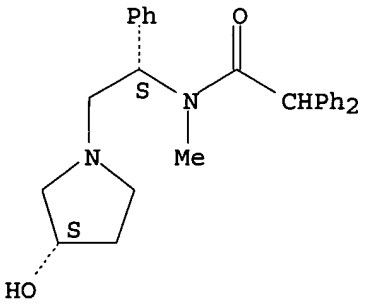
OTHER SOURCE(S): MARPAT 129:67799

IT **185951-07-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as kappa opioid receptor agonists)

RN 185951-07-9 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



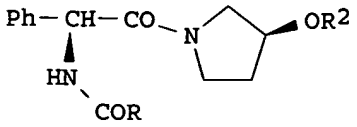
● HCl

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 46 OF 58 HCAPLUS

ED Entered STN: 04 Jun 1998

GI



I

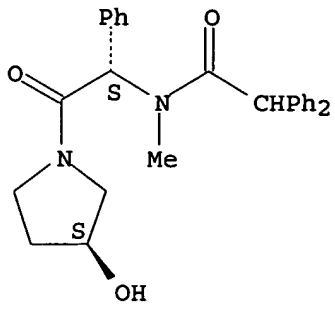
AB A new method is described for the preparation of N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or N-methyl-N-[(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide as well as the new compds. N-methyl-N-(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethane and N-methyl-N-(1R)-1-phenyl-2-((3R)-3-hydroxypyrrolidin-1-yl)ethane which are intermediates. The intermediates were prepared by hydrolysis of the reaction products of I (R = H, OR1 where R1 = C1-6-alkyl, aryl, heteroaryl, SiR33, COR3 (R3 = H, C1-6-alkyl, aryl, heteroaryl); R2 = H, C1-6-alkyl, aryl, heteroaryl, SiR33, COR3), prepared from the resp. pyrrolidine derivative and resp. N-substituted phenylglycine.

ACCESSION NUMBER: 1998:335043 HCAPLUS
DOCUMENT NUMBER: 129:27886
TITLE: Procedure for production of enantiomerically pure N-methyl-N-[1-phenyl-2-(3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide
INVENTOR(S): Bathe, Andreas; Helfert, Bernd; Ackermann, Karl-August; Gottschlich, Rudolf; Stein, Inge; Budak, Jens
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19647538	A1	19980520	DE 1996-19647538	19961116

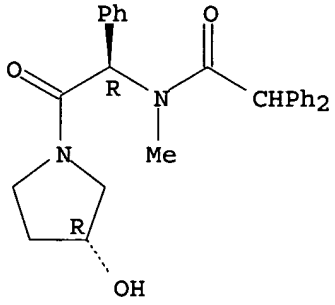
PRIORITY APPLN. INFO.: DE 1996-19647538 19961116
OTHER SOURCE(S): MARPAT 129:27886
IT **207847-94-7P 207847-95-8P**
RL: IMF (Industrial manufacture); PREP (Preparation)
(preparation from pyrrolidine derivative and phenylglycines)
RN 207847-94-7 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-2-oxo-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 207847-95-8 HCAPLUS
CN Benzeneacetamide, N-[(1R)-2-[(3R)-3-hydroxy-1-pyrrolidinyl]-2-oxo-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



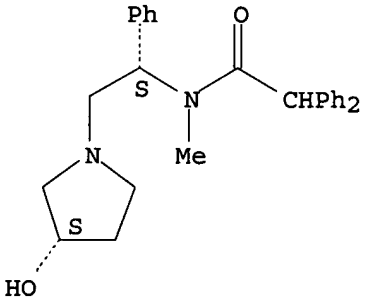
L4 ANSWER 47 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 29 May 1998
AB The objective of this study was to evaluate the effects of kappa-opioid receptor agonists on pressor and visceromotor responses to colorectal distension in awake, unrestrained rats, a model of visceral pain. Because visceral pain can be enhanced in the presence of inflammation, the study was conducted in rats that had been given either intracolonic saline or 5% acetic acid 6 h before drug administration. We developed a method of staircase colorectal distension as a means of obtaining stimulus-response functions over a short period of time. Kappa-opioid receptor agonists, given i.v. in a cumulative dose paradigm, dose-dependently attenuated both the pressor and visceromotor responses to colorectal distension. In addition, all drugs tested also increased response threshold. The rank order of potency of the drugs tested was: Cl977 > U69,593 > U50,488 ≥ morphine ≥ EMD61,753 > ICI204,448. EDs of these drugs were antagonized by naloxone, but not by either of two kappa-opioid receptor-selective antagonists (nor-binaltorphimine and 2-(3,4-dichlorophenyl)-N-methyl-N-(1-[3-isothiocyanate phenyl]-2-[1-pyrrolidinyl]ethyl)-acetamide). Acute inflammation of the colon did not lead to changes in the potency of the agonists tested. The present results provide further evidence that kappa-opioid receptor agonists significantly attenuate visceral nociception and, in conjunction with other information, suggest that a peripherally restricted kappa-opioid receptor agonist would be therapeutically effective in relieving visceral pain.
ACCESSION NUMBER: 1998:319400 HCAPLUS

Young, Shawquia

08/06/2006

DOCUMENT NUMBER: 129:62858
TITLE: Effects of kappa-opioid receptor agonists on responses to colorectal distension in rats with and without acute colonic inflammation
AUTHOR(S): Burton, Maureen B.; Gebhart, G. F.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, IA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1998), 285(2), 707-715
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0**, EMD61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kappa-opioid receptor agonists significantly attenuate visceral nociception)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



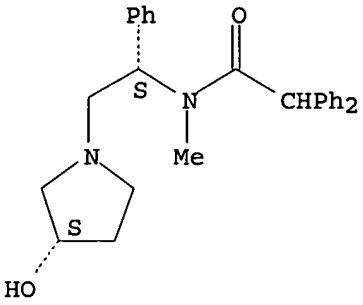
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 48 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 16 Feb 1998
AB The influence of the P-glycoprotein (Pgp) substrates digoxin, ondansetron, cyclosporin A, vinblastine, and dexamethasone on brain concns. of asimadoline, a peripherally selective .vkappa.-opioid agonist and Pgp substrate, was investigated in mice. Due to a plateau phase of brain concns. (radioactivity and parent drug) 15-30 min after administration, the time schedule above was chosen for coadministration of asimadoline and Pgp substrates. In the brain, concns. of parent drug and radioactivity showed no differences when coadministered with Pgp substrates. Thus, an influence of coadministered Pgp substrates on the brain concentration of asimadoline is unlikely.
ACCESSION NUMBER: 1998:89564 HCAPLUS
DOCUMENT NUMBER: 128:136113
TITLE: Brain concentrations of asimadoline in mice. The influence of coadministration of various P-glycoprotein substrates
AUTHOR(S): Bender, H. M.; Dasenbrock, J.
CORPORATE SOURCE: Inst. Pharmacokinetics Metabolism, Merck K.-G.a.A.,

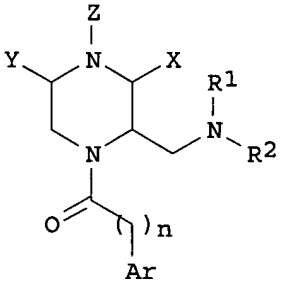
Grafing, D-85567, Germany
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (1998), 36(2), 76-79
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(brain concns. of asimadoline in mice. The influence of coadministration of various P-glycoprotein substrates)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 49 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 03 Dec 1997
GI



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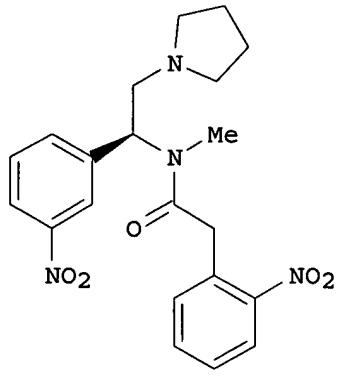


II

AB Compds. having kappa opioid agonist activity, compns. containing them, and methods of using them as analgesics are provided. The compds. have 4 general structures, e.g., I [n = 1-3; R1 = R2 = Me; or NR1R2 forms various cyclic systems; Ar = (un)substituted Ph, benzothienyl, benzofuranyl,

naphthyl, CHPh2, or 9-fluorenyl; Z = wide variety of sidechains; X, Y = various derivs. of CH2OH and CH2NH2]. A large number of compds., as HCl salts and/or free bases, were prepared, tested, and/or claimed. For instance, title compound II.HCl, i.e. ADL-01-0115-4, was prepared in 51% yield by amidation of 2-nitrophenylacetic acid with the corresponding secondary amine using DCC and pyridine in CH2Cl2. In tests for displacement of [3H]-diprenorphin or [3H]-U-69593 from kappa receptors in vitro, II.HCl had Ki values of 35 and 3.2 nM, resp.

ACCESSION NUMBER: 1997:752779 HCAPLUS
DOCUMENT NUMBER: 128:34783
TITLE: Kappa agonist compounds (acylpiperazines and analogs) and pharmaceutical formulations thereof
INVENTOR(S): Kruse, Lawrence I.; Chang, An-chih; Dehaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan
PATENT ASSIGNEE(S): Adolor Corp., USA
SOURCE: U.S., 65 pp., Cont.-in-part of U.S. Ser. No. 612,680. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 8
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5688955	A	19971118	US 1997-796078	19970205
US 5646151	A	19970708	US 1996-612680	19960308
CA 2240728	AA	19970912	CA 1997-2240728	19970301
CA 2240728	C	20051018		
AU 9721954	A1	19970922	AU 1997-21954	19970301
AU 717126	B2	20000316		
BR 9707958	A	20000104	BR 1997-7958	19970301
JP 2002502362	T2	20020122	JP 1997-531886	19970301
JP 3522767	B2	20040426		
US 5763445	A	19980609	US 1997-891833	19970714
US 5744458	A	19980428	US 1997-899086	19970723
US 5945443	A	19990831	US 1998-34661	19980303
US 5981513	A	19991109	US 1998-45522	19980321
NO 9804107	A	19981109	NO 1998-4107	19980907
NO 313194	B1	20020826		
US 6303611	B1	20011016	US 1998-150369	19980909
US 6057323	A	20000502	US 1998-183011	19981030
US 6028063	A	20000222	US 1999-307517	19990507
US 6054445	A	20000425	US 1999-307387	19990507
US 6239154	B1	20010529	US 1999-372191	19990811
US 6180623	B1	20010130	US 1999-436057	19991108
US 6391910	B1	20020521	US 2000-478482	20000106
US 2002042399	A1	20020411	US 2001-769450	20010126
US 2002013296	A1	20020131	US 2001-803957	20010313
US 6486165	B2	20021126		
US 2002103164	A1	20020801	US 2001-803976	20010313
US 6476063	B2	20021105		
US 6492351	B1	20021210	US 2001-803901	20010313
NO 2001004219	A	19981109	NO 2001-4219	20010831
NO 313633	B1	20021104		
NO 2001004220	A	19981109	NO 2001-4220	20010831
NO 313634	B1	20021104		
US 38133	E	20030603	US 2002-66909	20020204
US 2003144272	A1	20030731	US 2002-146693	20020515

US 6750216	B2	20040615		
US 2003236248	A1	20031225	US 2003-455545	20030605
US 2004220112	A1	20041104	US 2003-455687	20030605
US 6960612	B2	20051101		
US 2005020576	A1	20050127	US 2004-807113	20040323

PRIORITY APPLN. INFO.:

US 1996-612680	A2 19960308
US 1997-796078	A 19970205
WO 1997-US3353	W 19970301
US 1997-891833	A3 19970714
US 1997-899086	A3 19970723
US 1998-34661	A2 19980303
US 1998-45522	A3 19980321
US 1998-150369	A2 19980909
US 1998-183011	A3 19981030
US 1999-307517	A3 19990507
US 1999-372191	A3 19990811
US 1999-436057	A1 19991108
US 2000-478482	A2 20000106
US 2001-769450	A3 20010126
US 2002-146693	A1 20020515

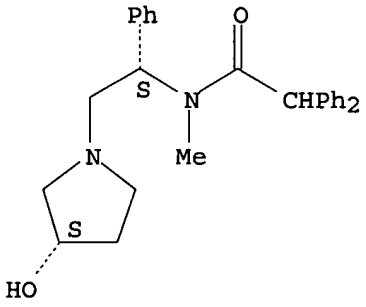
OTHER SOURCE(S): MARPAT 128:34783

IT **185951-07-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of acylpiperazines and analogs as kappa agonists)

RN 185951-07-9 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L4 ANSWER 50 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN

ED Entered STN: 08 Nov 1997

AB A review with 136 refs. Despite the recent introduction of a number of new compds., there has of late been a cooling of interest by pharmaceutical companies in the development of centrally-active, selective kappa opioid agonists for therapeutic purposes. This is reflected in the discontinuation of a number of clin. trials, for reasons that are often not completely clear to outside observers. Spiradoline and enadoline have apparently been abandoned as potential analgesics because they induce dose-limiting central side-effects (i.e., dysphoria) in models of

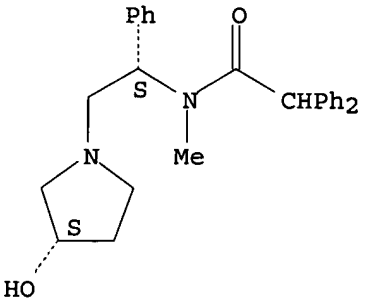
post-surgical pain. The development of niravoline as an aquaretic for the treatment of cirrhosis with ascites and other hyponatremic disorders has also been halted. Enadoline may yet find some application against ischemic stroke and severe head injury, presumably in comatose patients in whom psychiatric side-effects are taken to be immaterial, while apadoline and TRK 820 remain in Phase II clin. testing against cancer pain. The peripherally-selective kappa agonists, asimadoline, and the atypical compound, fedotozine, are well-tolerated in man. Results of Phase III trials of fedotozine against irritable bowel syndrome and dyspepsia have, however, ultimately been disappointing, whereas asimadoline is currently in Phase II clin. trials against pain of rheumatic and osteoarthritic origin. The results of these trials are eagerly awaited.

ACCESSION NUMBER: 1997:706772 HCAPLUS
DOCUMENT NUMBER: 128:18278
TITLE: Novel developments with selective, non-peptidic kappa-opioid receptor agonists
AUTHOR(S): Barber, Andrew; Gottschlich, Rudolf
CORPORATE SOURCE: Department of CNS Research, Preclinical Pharmaceutical Research, Merck KGaA, Darmstadt, 64271, Germany
SOURCE: Expert Opinion on Investigational Drugs (1997), 6(10), 1351-1368
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

IT **153205-46-0**, Asimadoline
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel developments with selective, non-peptidic kappa-opioid receptor agonists as analgesics)

RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 137 THERE ARE 137 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 51 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 10 Apr 1997
AB N-methyl-N-[(1S)-1-phenyl-2-[(3S)-3-hydroxypyrrolidin-1-yl]ethyl]-2,2-diphenylacetamide (EMD-61753), a κ-opioid antagonist for treatment of inflammatory bowel disease, hyperalgesia, burns, neurodermatitis, and rheumatic disorders, is prepared in a highly thermostable crystalline modification designated type IV (m. 220-225°) by condensation of

1-[(1S)-3-hydroxypyrrolidin-1-yl]-(2S)-2-methylamino-2-phenylethane with diphenylacetyl chloride at low temperature (preferably 0-8°). Type IV is also formed during prolonged storage of type II at 170°, or by rapid cooling of a melt of type II from >200° and storage at room temperature for 12-16 h. Prepns. containing EMD-61753 type IV can be sterilized.

Thus, suppositories were prepared from a melt of EMD-61753 20, soybean lecithin 100, and cocoa butter 1400 g.

ACCESSION NUMBER: 1997:231063 HCAPLUS
DOCUMENT NUMBER: 126:216665
TITLE: Thermostable form of EMD-61753
INVENTOR(S): Stein, Inge; Beeres, Holger; Beschmann, Klaus; Neuenfeld, Steffen
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 5 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

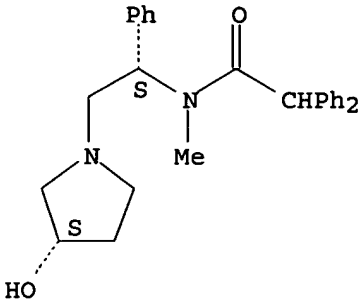
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19531464	A1	19970227	DE 1995-19531464	19950826
EP 761650	A1	19970312	EP 1996-112489	19960802
EP 761650	B1	20011031		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 207895	E	20011115	AT 1996-112489	19960802
ES 2165948	T3	20020401	ES 1996-112489	19960802
PT 761650	T	20020429	PT 1996-112489	19960802
CZ 287783	B6	20010214	CZ 1996-2434	19960816
AU 9662149	A1	19970306	AU 1996-62149	19960819
AU 716615	B2	20000302		
JP 09110830	A2	19970428	JP 1996-221296	19960822
SK 282437	B6	20020205	SK 1996-1089	19960822
CA 2184049	AA	19970227	CA 1996-2184049	19960823
NO 9603526	A	19970227	NO 1996-3526	19960823
NO 307048	B1	20000131		
ZA 9607200	A	19970303	ZA 1996-7200	19960823
CN 1151986	A	19970618	CN 1996-111404	19960823
CN 1081631	B	20020327		
BR 9603540	A	19980512	BR 1996-3540	19960823
RU 2174976	C2	20011020	RU 1996-116925	19960823
TW 513407	B	20021211	TW 1996-85110305	19960823
PL 187691	B1	20040930	PL 1996-315799	19960823
US 6060504	A	20000509	US 1996-703350	19960826

PRIORITY APPLN. INFO.: DE 1995-19531464 A 19950826
OTHER SOURCE(S): CASREACT 126:216665

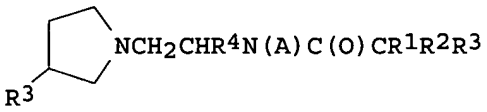
IT **153205-46-0P**, EMD-61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thermostable form of EMD-61753)

RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 52 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 12 Feb 1997
GI



I

AB The title compds. [I; R1 = aryl, C3-7 cycloalkyl, C4-8 cycloalkylalkyl; R2 = aryl; R3 = H, OH, alkyl, alkoxy; R4 = alkyl, (substituted) Ph; R5 = OH, CH2OH; A = C1-7 alkyl] and their salts and glycosylated derivs. are useful in treatment of inflammatory bowel disease to relieve pain and restore normal bowel motility, as well as in treatment of ileus and neurodermitis. Thus, tablets containing 10 mg I were prepared from a mixture containing I 1, lactose 4, potato starch 1.2, talc 0.2, and Mg stearate 0.1 kg.

ACCESSION NUMBER: 1997:97208 HCAPLUS
DOCUMENT NUMBER: 126:108937
TITLE: N-(pyrrolidinoethyl)arylacetamides as κ-opiate agonists for treatment of inflammatory bowel disease
INVENTOR(S): Barber, Andrew; Seyfried, Christoph; Bartoszyk, Gerd; Gottschlich, Rudolf
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: Ger. Offen., 7 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19523502	A1	19970102	DE 1995-19523502	19950628
EP 752246	A2	19970108	EP 1996-109915	19960620
EP 752246	A3	19970226		
EP 752246	B1	20020313		
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 214275	E	20020315	AT 1996-109915	19960620
ES 2171577	T3	20020916	ES 1996-109915	19960620
PT 752246	T	20020930	PT 1996-109915	19960620
AU 9656162	A1	19970109	AU 1996-56162	19960624

AU 708699	B2	19990812			
CZ 289805	B6	20020417	CZ 1996-1866		19960625
CA 2179955	AA	19961229	CA 1996-2179955		19960626
JP 09020659	A2	19970121	JP 1996-165988		19960626
RU 2190401	C2	20021010	RU 1996-112771		19960626
NO 9602720	A	19961230	NO 1996-2720		19960627
NO 309674	B1	20010312			
ZA 9605480	A	19970127	ZA 1996-5480		19960627
CN 1145781	A	19970326	CN 1996-110142		19960627
CN 1119147	B	20030827			
BR 9602915	A	19980422	BR 1996-2915		19960627
US 5776972	A	19980707	US 1996-671502		19960627
TW 430557	B	20010421	TW 1996-85107762		19960627
PL 185537	B1	20030530	PL 1996-314996		19960627
SK 283497	B6	20030805	SK 1996-843		19960627
US 5977161	A	19991102	US 1998-27228		19980220
PRIORITY APPLN. INFO.:			DE 1995-19523502	A	19950628
			US 1996-671502	A3	19960627

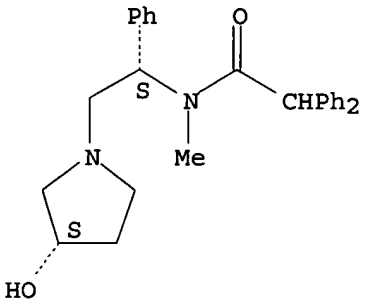
OTHER SOURCE(S): MARPAT 126:108937

IT **185951-07-9 185951-07-9D**, glycosylated derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-(pyrrolidinoethyl)arylacetamides as κ-opiate agonists for treatment of inflammatory bowel disease)

RN 185951-07-9 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

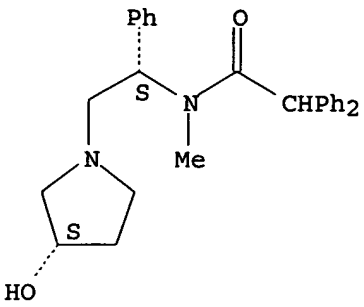


● HCl

RN 185951-07-9 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

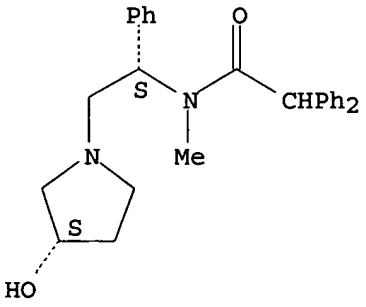
L4 ANSWER 53 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 16 Jul 1996
AB Several heterocyclic bicyclo[3.3.1]nonan-9-ones were found to have a high affinity to κ opioid receptors. 3,7-Diazabicyclononanones with 2,4-dipyridyl side chains were the most potent agonists whereas the corresponding 3-oxa-7-azabicyclo[3.3.1]nonan-9-one and compds. with Ph substituents in 2 and 4 position are almost inactive. The purpose of this study was to unravel the active conformation of the bicyclononanones using well-known κ-selective agonists such as ketocyclacocine, arylacetamides, several isoquinolines, CI-977, and four stereoisomers of EMD-61753 for comparison. In order to determine the geometry of the diazabicycles in solution pH-dependent NMR measurements of the bicycles were recorded and the results were related to the geometries of the aforementioned κ agonists obtained from semiempirical PM3 calcns. A chair-boat conformation and a protonation at the N7 nitrogen atom of the diazabicyclononanones were found to be the pharmacophoric conformation. Comparison of the spatial arrangements, electrostatic, hydrophobic, and hydrogen bonding potentials of all κ-selective agonists led to a model of structure-activity relationships of ligands of the κ receptor. The arrangement of the pharmacophoric elements is characterized by an almost parallel orientation of a carbonyl and a protonated NH function in conjunction with at least one aromatic ring. Ketocyclazocine is only able to adopt this parallel orientation when the nitrogen is inverted relative to the x-ray structure. Furthermore, two binding sites for the aromatic rings are discussed. The pharmacol. results of all considered bicyclononanone derivs. as well as of the four enantiomers of EMD-61753 can be understood and consistently explained in this way.

ACCESSION NUMBER: 1996:411968 HCAPLUS
DOCUMENT NUMBER: 125:104282
TITLE: Search for the pharmacophore in kappa-agonistic diazabicyclo[3.3.1]nonan-9-one-1,5-diesters and arylacetamides
AUTHOR(S): Brandt, Wolfgang; Drosihn, Susanne; Haurand, Michael; Holzgrabe, Ulrike; Nachtsheim, Corina
CORPORATE SOURCE: Pharm. Inst., Univ. bonn, Bonn, 53115, Germany
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1996), 329(6), 311-323
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English

08/06/2006

IT **153205-46-0**, EMD-61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore in κ-agonistic diazabicyclo[3.3.1]nonan-9-one-1,5-diesters and arylacetamides)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



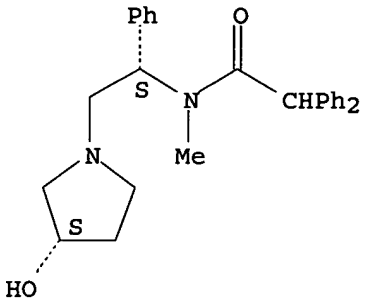
L4 ANSWER 54 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 25 Jan 1996
AB EMD 61753 (N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)-ethyl]2,2-diphenylacetamide hydrochloride) is a peripherally selective κ-opiate agonist. It exhibits antihyperalgesic activity in animal models of inflammatory pain at doses which do not cause signs of central action. The structure of this compound was varied in different ways and the resulting derivs. were tested for affinity to the κ-receptor. Furthermore, those compds. with binding values comparable to that of EMD 61753 were tested for central activity. This was done by measuring the extent to which the haloperidol-induced L-DOPA accumulation in the nucleus accumbens of the rat could be reversed after application of 10 mg/kg s.c. of the test compound Structure-activity relationships revealed that none of the analogs or reference compds. tested is superior to the parent compound with regard to its favorable ratio between κ-receptor affinity and peripheral selectivity.
ACCESSION NUMBER: 1996:51690 HCAPLUS
DOCUMENT NUMBER: 124:193280
TITLE: The peripherally acting κ-opiate agonist EMD 61753 and Analogs: opioid activity versus peripheral selectivity
AUTHOR(S): Gottschlich, R.; Barber, A.; Bartoszyk, G. D.; Seyfried, C. A.
CORPORATE SOURCE: Preclinical Pharmaceutical Research, E. Merck, Darmstadt, D-64271, Germany
SOURCE: Drugs under Experimental and Clinical Research (1995), 21(5), 171-4
CODEN: DECRDP; ISSN: 0378-6501
PUBLISHER: Bioscience Ediprint
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0D**, EMD 61753, analogs **153205-47-1** **161496-48-6** **174502-29-5** **174502-30-8** **174502-34-2**

Young, Shawquia

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(κ-opiate agonist EMD 61753 and analogs structure-related opioid activity vs. peripheral selectivity)

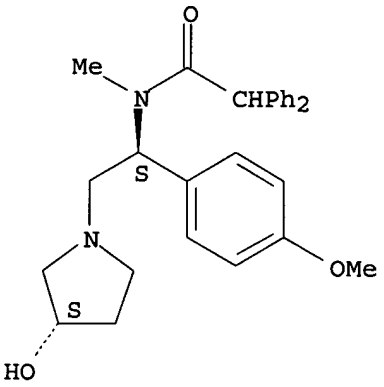
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



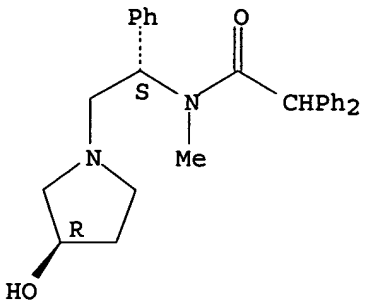
RN 153205-47-1 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-(4-methoxyphenyl)ethyl]-N-methyl-α-phenyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



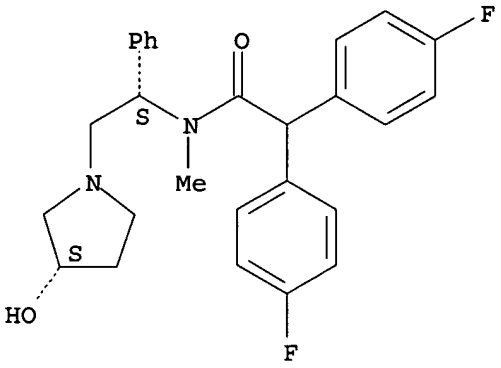
RN 161496-48-6 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-α-phenyl-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



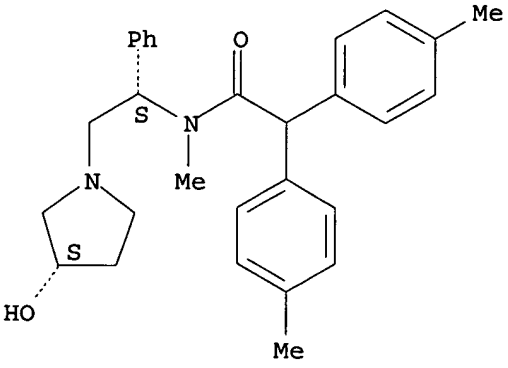
RN 174502-29-5 HCAPLUS
CN Benzeneacetamide, 4-fluoro-α-(4-fluorophenyl)-N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



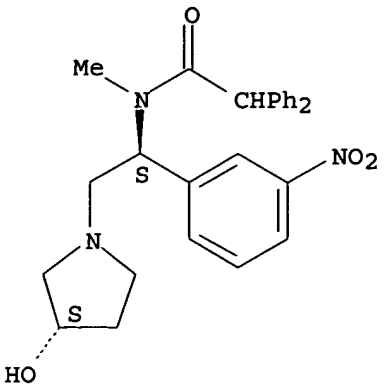
RN 174502-30-8 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N,4-dimethyl-α-(4-methylphenyl)-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



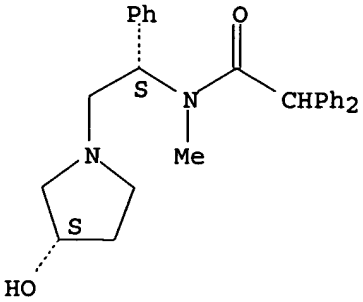
RN 174502-34-2 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-(3-nitrophenyl)ethyl]-N-methyl-α-phenyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



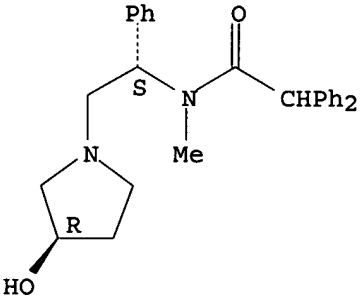
L4 ANSWER 55 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 12 Jan 1995
AB The four stereoisomers of the two peripherally selective κ-opioid agonists EMD 60 400 and EMD 61 753 were examined for affinity to the κ opioid receptor. The relationships between the configuration of these mols. and their biol. activity are discussed.
ACCESSION NUMBER: 1995:293027 HCAPLUS
DOCUMENT NUMBER: 122:177671
TITLE: K-opioid activity of the four stereoisomers of the peripherally selective κ-agonists, EMD 60 400 and EMD 61 753
AUTHOR(S): Gottschlich, Rudolf; Krug, Michael; Barber, Andrew; Devant, Ralf M.
CORPORATE SOURCE: Dep. Medicinal Chem. Biological Res., E. Merck, Darmstadt, Germany
SOURCE: Chirality (1994), 6(8), 685-9
CODEN: CHRLEP; ISSN: 0899-0042
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0 161496-48-6 161496-49-7 161496-50-0**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(κ-opioid activity of stereoisomers of peripherally selective κ-agonists, EMD 60 400 and EMD 61 753)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



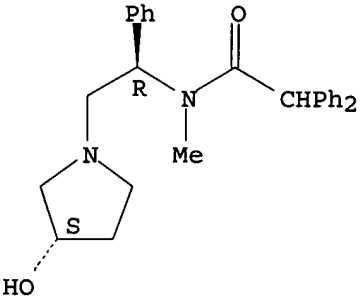
RN 161496-48-6 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-α-phenyl-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



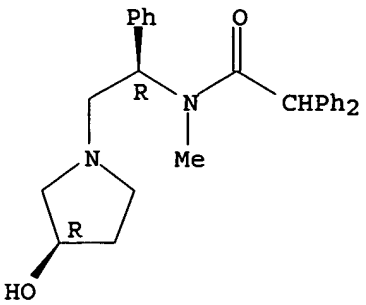
RN 161496-49-7 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-α-phenyl-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 161496-50-0 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-α-phenyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 56 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 17 Dec 1994
AB The pharmacol. properties of the novel diarylacetamide κ-opioid receptor agonist, EMD 61753, have been compared with those of ICI 197067 (a centrally-acting κ agonist) and ICI 204448 (a peripherally-selective κ agonist). EMD 61753 binds with high affinity (IC50 5.6 nM) and selectivity (κ:μ:δ:σ binding ratio 1:536:125:>1,786) to κ-opioid receptors and is a full and potent (IC50 54.5 nM) agonist in an in vitro assay for κ-opioid receptors (rabbit vas deferens preparation). Systemically-applied [14C]-EMD 61753 is found in high concns. in the lungs, liver, adrenal glands and kidneys. Considerably less radioactivity is detected in the whole brain, and this radioactivity is concentrated in the region of the cerebral ventricles in the choroid plexuses. EMD 61753 penetrates only poorly into the CNS. EMD 61753 was weakly effective in pharmacol. tests of central activity. This compound reversed haloperidol-induced DOPA accumulation in the nucleus accumbens of the rat only at a dose of 30 mg kg-1, s.c., (doses of 0.1, 1.0 and 10 mg kg-1, s.c., and 1.0, 10 and 100 mg kg-1, p.o., were inactive). Hexobarbitone-induced sleeping in mice was prolonged by EMD 61753 at threshold doses of 10 mg kg-1, s.c., and 100 mg kg-1, p.o., whereas the motor performance of rats in the rotorod test was impaired by EMD 61753 with an ID50 value of 453 mg kg-1, s.c. EMD 61753 produced dose-dependent, naloxone-reversible, antinociception in the mouse formalin test (1st phase ID50 1.9 mg kg-1, s.c., and 10.4 mg kg-1, p.o.: 2nd phase ID50 0.26 mg kg-1, s.c., and 3.5 mg kg-1, p.o.) and rodent abdominal constriction test (ID50 mouse 1.75 mg kg-1, s.c., and 8.4 mg kg-1, p.o.; ID50 rat 3.2 mg kg-1, s.c., and 250 mg kg-1, p.o.). EMD 61753 was inactive, or only weakly effective, in the rat pressure test under normalgesic conditions. After the induction of hyperalgesia with carrageenin, however, this compound elicited potent, dose-dependent (ID50 0.08 mg kg-1, p.o., after prophylactic application) and naloxone-reversible antinociception. The antinociceptive action of systemically-applied (50 mg kg-1, p.o.) EMD 61753 in the hyperalgesic pressure test was completely inhibited by injection of the κ-opioid antagonist nor-binaltorphimine (100 μg) into the inflamed tissue, a result which indicates that this opioid effect is mediated peripherally. Cutaneous plasma protein extravasation produced by antidromic elec. stimulation of the rat saphenous nerve was dose-dependently inhibited by systemically-applied EMD 61753 (ID50 values 3.7 mg kg-1, s.c., and 35.8 mg kg-1, p.o.), and this effect was completely antagonized by intraplanar application of norbinaltorphimine (50 μg). Extravasation elicited by the intraplanar application of substance P (10 μg) was not influenced by the administration of EMD 61753. EMD 61753 produced dose-dependent diuresis in non-hydrated rats at doses of and above 1.0 mg kg-1, s.c., and 10 mg kg-1, p.o., and in saline-loaded rats at doses of and above 10 mg

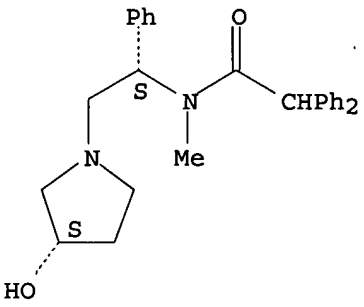
kg-1, s.c., and 30 mg kg-1, p.o. The prostaglandin-mediated fall in mean arterial blood pressure elicited in anesthetized rats by i.v. application of arachidonic acid was not inhibited by prior treatment with EMD 61753 (10 mg kg-1, p.o.). Thus, a blockade of prostaglandin synthesis via inhibition of cyclo-oxygenase activity does not contribute to the in vivo effects of EMD 61753 and its metabolites. The present expts. therefore indicate that EMD 61753 is a potent, selective and orally-effective full κ-opioid receptor agonist which has a limited ability to penetrate the blood-brain barrier and elicit centrally-mediated sedation, putative aversion, diuresis, and antinociception. The inhibitory actions of systemically-applied EMD 61753 against hyperalgesic pressure nociception and neurogenic inflammation are mediated peripherally, probably by opioid receptors on the endings of sensory nerve fibers.

ACCESSION NUMBER: 1995:252056 HCAPLUS
DOCUMENT NUMBER: 122:46289
TITLE: A pharmacological profile of the novel, peripherally-selective κ-opioid receptor agonist, EMD 61753
AUTHOR(S): Barber, A.; Bartoszyk, G. D.; Bender, H. M.; Gottschlich, R.; Greiner, H. G.; Harting, J.; Mauler, F.; Minck, K.-O.; Murray, R. D.; et al.
CORPORATE SOURCE: Preclinical Pharmaceutical Res., E. Merck, Darmstadt, 64271, Germany
SOURCE: British Journal of Pharmacology (1994), 113(4), 1317-27
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English

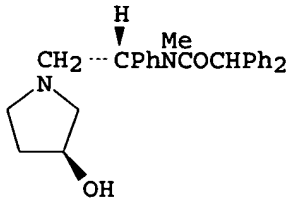
IT **153205-46-0**, EMD 61753
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. profile of novel, peripherally-selective κ-opioid receptor agonist, EMD 61753)

RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 57 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 20 Aug 1994
GI

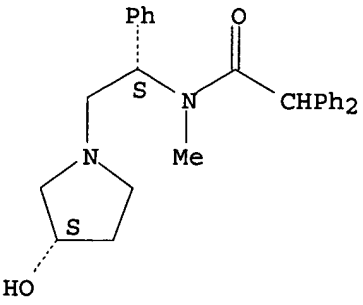


I

AB κ Opiate agonists like (-)-U50488H, (-)-PD 117302, etc., contain an acetamido group which is monosubstituted in the α-position by an aromatic moiety. In contrast, EMD 61753 (I) is disubstituted in this position by two Ph rings and is thus the first representative of the new class of diarylacetamide-type κ opiates. Derivs. of EMD 61753 are described and structure-activity relationships are discussed. In the formalin test in mice EMD 61753 shows a profile similar to that of the anti-inflammatory drugs rather than that of the centrally acting opiates.

ACCESSION NUMBER: 1994:473054 HCAPLUS
DOCUMENT NUMBER: 121:73054
TITLE: EMD 61753 as a favorable representative of structurally novel arylacetamido-type κ opiate receptor agonists
AUTHOR(S): Gottschlich, R.; Ackermann, K. A.; Barber, A.; Bartoszyk, G. D.; Greiner, H. E.
CORPORATE SOURCE: Med. Chem. Dep., E. Merck, Darmstadt, D-64271, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(5), 677-82
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **153205-46-0P**, EMD 61753 **156114-52-2P**
156114-56-6P 156114-57-7P 156114-58-8P
156114-65-7P 156114-66-8P 156114-67-9P
156114-68-0P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and κ-opiate agonist activity of)
RN 153205-46-0 HCAPLUS
CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

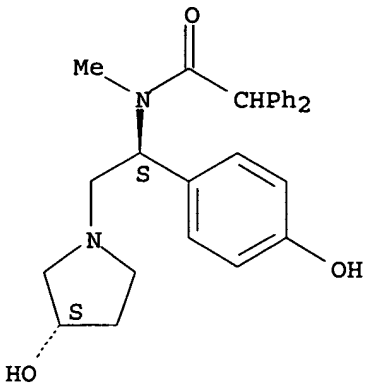
Absolute stereochemistry.



RN 156114-52-2 HCAPLUS
CN Benzeneacetamide, N-[1-(4-hydroxyphenyl)-2-(3-hydroxy-1-pyrrolidinyl)ethyl]-N-methyl-α-phenyl-, monohydrochloride,

[S-(R*,R*)]- (9CI) (CA INDEX NAME)

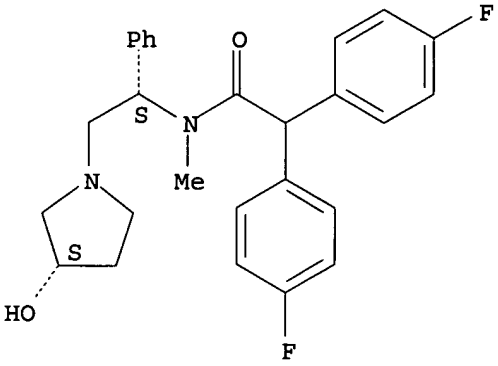
Absolute stereochemistry.



● HCl

RN 156114-56-6 HCAPLUS
CN Benzeneacetamide, 4-fluoro-α-(4-fluorophenyl)-N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-, monohydrochloride, [S-(R*,R*)]-(9CI) (CA INDEX NAME)

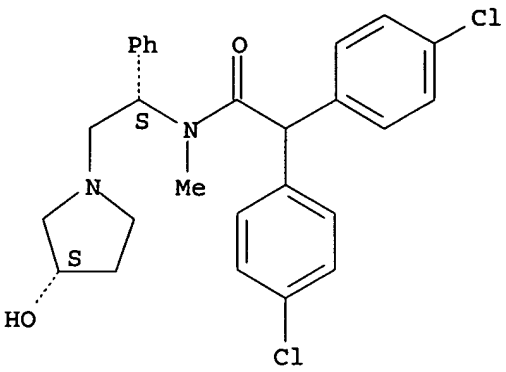
Absolute stereochemistry.



● HCl

RN 156114-57-7 HCAPLUS
CN Benzeneacetamide, 4-chloro-α-(4-chlorophenyl)-N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-, monohydrochloride, [S-(R*,R*)]-(9CI) (CA INDEX NAME)

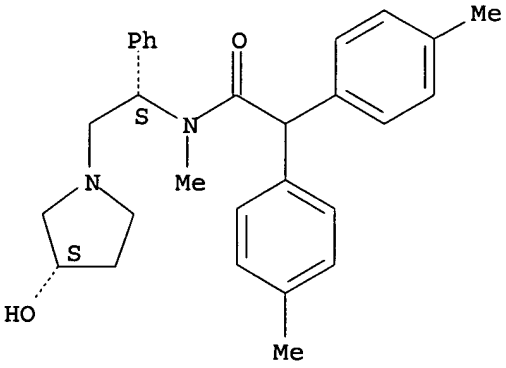
Absolute stereochemistry.



● HCl

RN 156114-58-8 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N,4-dimethyl-α-(4-methylphenyl)-, monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

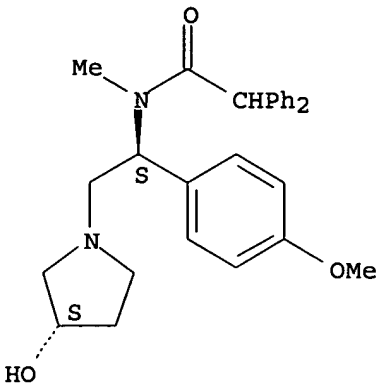
Absolute stereochemistry.



● HCl

RN 156114-65-7 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-(4-methoxyphenyl)ethyl]-N-methyl-α-phenyl-, monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

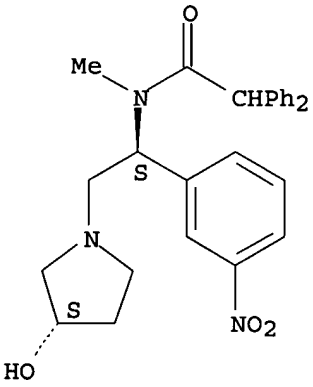
Absolute stereochemistry.



● HCl

RN 156114-66-8 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-(3-nitrophenyl)ethyl]-N-methyl-α-phenyl-, monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

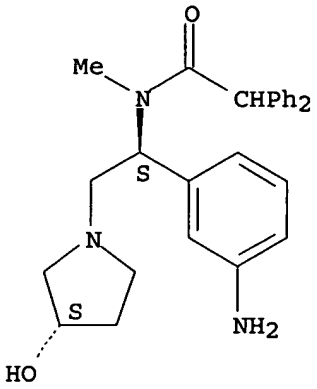
Absolute stereochemistry.



● HCl

RN 156114-67-9 HCAPLUS
CN Benzeneacetamide, N-[1-(3-aminophenyl)-2-(3-hydroxy-1-pyrrolidinyl)ethyl]-N-methyl-α-phenyl-, monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

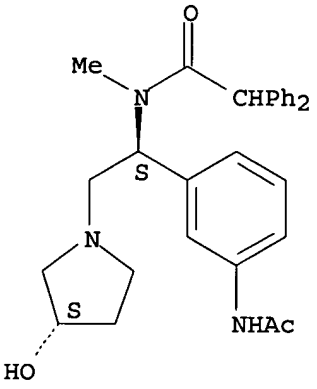
Absolute stereochemistry.



● HCl

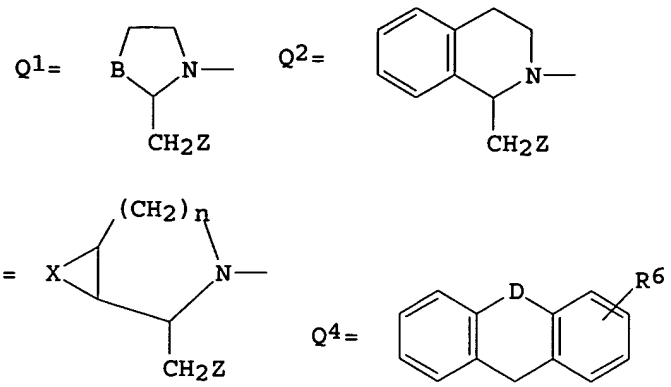
RN 156114-68-0 HCAPLUS
CN Benzeneacetamide, N-[1-[3-(acetylamino)phenyl]-2-(3-hydroxy-1-pyrrolidinyl)ethyl]-N-methyl-α-phenyl-, monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

L4 ANSWER 58 OF 58 HCAPLUS COPYRIGHT 2006 ACS on STN
ED Entered STN: 02 Apr 1994
GI



AB QCOCR1R2R3 [Q = R4CH(CH2Z)NA, Q1-Q3; R1 = aryl, cycloalkyl, cycloalkylalkyl; R2 = aryl; or R1R2 = Q4; R3 = H, OH, alkoxy, alkyl; R4 = alkyl, (substituted) Ph; R5, R6 = H, F, Cl, Br, iodo, OH, alkoxy, CF3, amino, ureido, NO2, methylenedioxy, etc; B = CH2, O, imino, bond; X = (substituted) condensed ring system; D = CH2, O, S, imino, CH2CH2, CH:CH, CH2O, bond, etc.; Z = (substituted) 1-pyrrolidinyl; n = 1, 2], were prepared as analgesics and neuroprotectants with a high affinity for κ-receptors (no data). Thus, diphenylacetyl chloride and (1S)-[1-N-methylamino-1-phenyl-2-[(3S)-3-hydroxypyrrolidino]]ethane were stirred in THF to give N-Me N-[(1S)-1-phenyl-2-[(3S)-3-hydroxypyrrolidino]ethyl]-2-diphenylacetamide. Dosage formulations were prepared containing several specific compds. of the invention.

ACCESSION NUMBER: 1994:163969 HCAPLUS
DOCUMENT NUMBER: 120:163969
TITLE: Preparation of (pyrrolidinoalkyl)arylacetamides as analgesics and neuroprotectants with high affinity for κ-ligands.
INVENTOR(S): Gottschlich, Rudolf; Ackermann, Karl August; Pruecher, Helmut; Seyfried, Christoph; Greiner, Hartmut; Bartoszyk, Gerd; Mauler, Frank; Stohrer, Manfred; Barber, Andrew
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4215213	A1	19931111	DE 1992-4215213	19920509
EP 569802	A1	19931118	EP 1993-107103	19930501
EP 569802	B1	19980715		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 168368	E	19980815	AT 1993-107103	19930501
ES 2121030	T3	19981116	ES 1993-107103	19930501
AU 9338341	A1	19931111	AU 1993-38341	19930503
AU 662051	B2	19950817		
CZ 289961	B6	20020515	CZ 1993-823	19930505
RU 2125041	C1	19990120	RU 1993-4806	19930506
CA 2095797	AA	19931110	CA 1993-2095797	19930507

NO 9301681	A	19931110	NO 1993-1681	19930507
NO 179789	B	19960909		
NO 179789	C	19961218		
ZA 9303222	A	19931208	ZA 1993-3222	19930507
HU 70172	A2	19950928	HU 1993-1325	19930507
HU 214578	B	19980428		
PL 173779	B1	19980430	PL 1993-298845	19930507
CN 1079219	A	19931208	CN 1993-105673	19930508
CN 1041087	B	19981209		
JP 06049022	A2	19940222	JP 1993-108444	19930510
JP 3210771	B2	20010917		
SK 282646	B6	20021008	SK 1993-468	19930512
US 5532266	A	19960702	US 1995-453811	19950530
PRIORITY APPLN. INFO.:			DE 1992-4215213	A 19920509
			US 1993-57801	B1 19930507

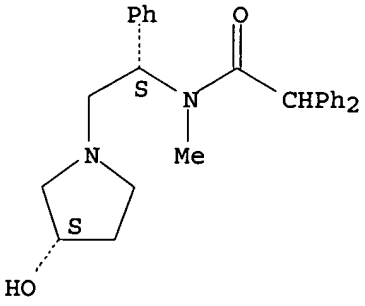
OTHER SOURCE(S): MARPAT 120:163969

IT **153205-46-0P 153205-47-1P 153205-60-8P**
153205-61-9P 153205-63-1P 153205-66-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as analgesic and neuroprotectant with high κ-receptor affinity)

RN 153205-46-0 HCAPLUS

CN Benzeneacetamide, N-[(1S)-2-[(3S)-3-hydroxy-1-pyrrolidinyl]-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

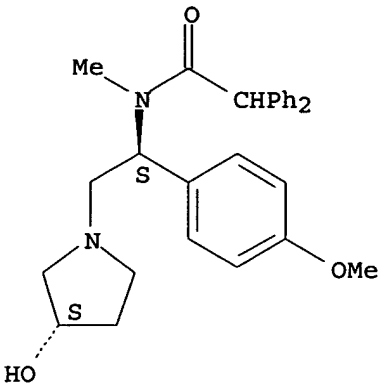
Absolute stereochemistry.



RN 153205-47-1 HCAPLUS

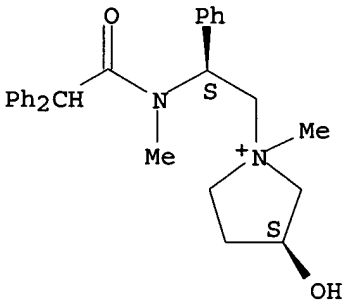
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-(4-methoxyphenyl)ethyl]-N-methyl-α-phenyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



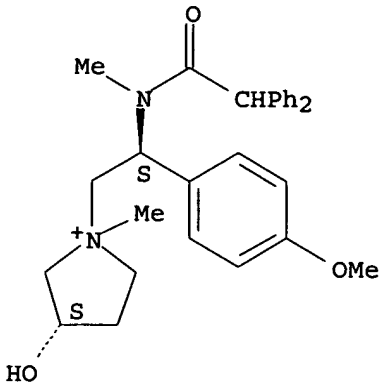
RN 153205-60-8 HCAPLUS
CN Pyrrolidinium, 1-[2-[(diphenylacetyl)methylamino]-2-phenylethyl]-3-hydroxy-1-methyl-, iodide, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

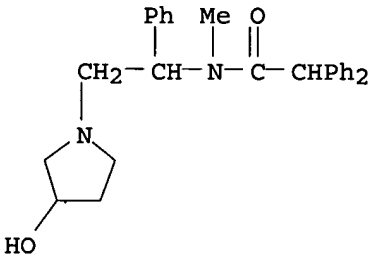


RN 153205-61-9 HCAPLUS
CN Pyrrolidinium, 1-[2-[(diphenylacetyl)methylamino]-2-(4-methoxyphenyl)ethyl]-3-hydroxy-1-methyl-, iodide, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

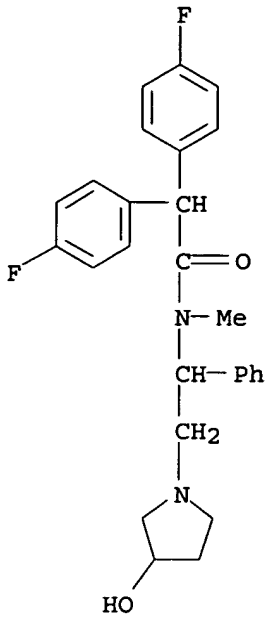
Absolute stereochemistry.



RN 153205-63-1 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl-α-phenyl- (9CI) (CA INDEX NAME)

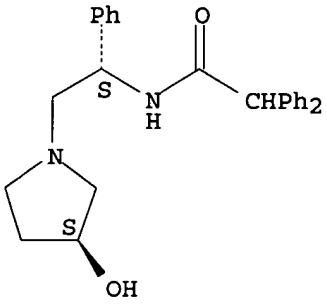


RN 153205-66-4 HCAPLUS
CN Benzeneacetamide, 4-fluoro-α-(4-fluorophenyl)-N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-N-methyl- (9CI) (CA INDEX NAME)



IT **153205-71-1 153205-73-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of arylacetamide analgesic and neuroprotectant with high κ-receptor affinity)
RN 153205-71-1 HCAPLUS
CN Benzeneacetamide, N-[2-(3-hydroxy-1-pyrrolidinyl)-1-phenylethyl]-α-phenyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

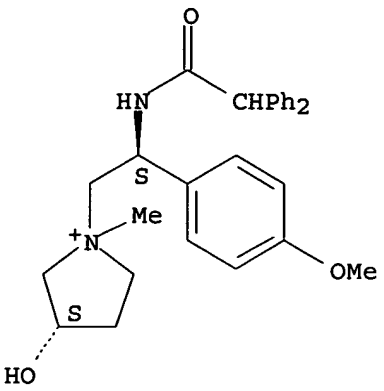
Absolute stereochemistry.



RN 153205-73-3 HCAPLUS
CN Pyrrolidinium, 1-[2-[(diphenylacetyl)amino]-2-(4-methoxyphenyl)ethyl]-3-hydroxy-1-methyl-, iodide, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

08/06/2006



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Executing the logoff script...


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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	304.90	472.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-42.75	-42.75

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STN INTERNATIONAL LOGOFF AT 09:24:22 ON 02 MAY 2006
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Young, Shawquia